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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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TITLE OF THE INVENTION (500 characters max)

CRYSTALS AND STRUCTURES OF p21-ACTIVATED KINASE 6

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☐ Application Data Sheet. *See 37 CFR 1.76*

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

FILING FEE AMOUNT ($)

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

DATE February 23, 2004

SIGNATURE

REGISTRATION NO. *(if appropriate)* 40,812

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Docket No. PT145/01.PRO

CERTIFICATE OF MAILING (37 CFR 1.10)

I hereby certify that the attached Provisional Application Cover Sheet and associated documents attached thereto are being deposited with the United States Postal Service on this date in an envelope as "Express Mail Post Office to Addressee" addressed to: Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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NEW APPLICATION

THE UNITED STATES

PATENT AND TRADEMARK OFFICE

FOR

CRYSTALS AND STRUCTURES OF p21-ACTIVATED KINASE 6

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CRYSTALS AND STRUCTURES OF p21-ACTIVATED KINASE 6

INTRODUCTION

[0001] The present invention concerns crystalline forms of polypeptides that correspond to the kinase domain of p21-activated kinase 6 (PAK6KD), methods of obtaining such crystals, and to the high-resolution X-ray diffraction structures and molecular structure coordinates obtained therefrom. The crystals of the invention and the atomic structural information obtained therefrom are useful, for example, for solving the crystal and solution structures of related and unrelated proteins, for screening for, identifying, and/or designing protein analogues and modified proteins, and for screening for, identifying and/or designing compounds that bind to and/or modulate a biological activity of PAK6, including inhibitors and activators of PAK6 activity.

[0002] PAK6 (p21-activated kinase 6) is a kinase in the STE group of serine/threonine kinases. It is a member of the group II PAKs, which comprises PAK4, PAK5, and PAK6 (Jaffer, Z. M., and Chernoff, J., *J. Biochem Cell Bio.*, 34:713-717, 2002). The PAKs contain an N-terminal p21-Rho-binding domain and a C-terminal catalytic protein kinase domain. Both PAK groups have been implicated in actin reorganization, gene transcription, and apoptosis, while the group II PAKs have also been implicated in cell transformation and hormone signaling (Jaffer and Chernoff, 2002). PAK6 interacts with at least two nuclear hormone receptors; it is recruited to the nucleus in the presence of ligand-bound androgen receptor (AR) (Yang, F., et al., *J. Biol. Chem*, 276:15345-15353, 2001) and it is able to bind Erα (Lee, S. R., et al., *Mol. Endocrinol.* 16:85-99, 2002). Binding of PAK6 to AR appears to repress transcription by preventing coactivator binding. This may be a novel mechanism within the PAK family and has implications for the treatment of prostate and breast cancer. Unphosphorylated (active) PAK6 has recently been shown to be differentially expressed in prostate cancer cell lines (Schrantz, N., et al., *J. Biol. Chem*, 279:1922-1931, 2004).

[0003] The present invention describes the 3-dimensional structure of the kinase domain of PAK6 (PAK6KD). The 3 dimensional structure of PAK6 may be useful, for example, for identifying novel therapeutic compounds that can modulate protein kinase activity, and for treatment of diseases or conditions mediated by human signal transduction kinase activity, or diseases or conditions that may be alleviated or prevented

by modulation of, PAK6 activity, and/or, for example, actin reorganization, gene transcription, apoptosis, hormone signaling, or cell transformation.

[0004] Knowledge of the 3-D structures of target proteins provides an important basis for structure-based approaches to drug design by defining the topographies of the complementary surfaces of ligands and their protein targets. Therefore, knowledge of the structure of the PAK6KD protein described in the present invention may be useful in the identification, design, or development of novel and specific modulators of protein kinase activity as well as diagnostic and pharmaceutical compounds useful for disorders associated with aberrant PAK6 expression or activity. Knowledge of the structure may also be useful for gene therapy. The structural coordinates may be used, for example, to engineer more stable or other modified PAK6s. The ability to obtain the molecular structure coordinates of PAK6KD has not previously been realized.

[0005] Citation of documents herein is not intended as an admission that any is pertinent prior art. All statements as to the date or representation as to the contents of documents is based on the information available to the applicant and does not constitute any admission as to the correctness of the dates or contents of the documents.

SUMMARY OF THE INVENTION

[0006] The present invention provides crystalline PAK6KD, its molecular structure in atomic detail, homologs and mutants of the structure, methods of using the structure to identify and design compounds that modulate the activity of PAK6, methods of preparing identified and/or designed compounds, methods of affecting cell growth and/or viability, and thus treating diseases or conditions, by modulating PAK6 activity, and methods of identifying and designing mutant PAK6s. Knowledge of the structure of PAK6KD may be useful in the development of novel compounds regulating, for example, cell proliferation, cell migration, differentiation, cytoskeletal organization, gene expression, cell cycle progression, and cell death. Knowledge of the structure of PAK6KD may also be used to model the structure of kinases with related ligand binding sites, such as, for example, other PAKs.

[0007] By "PAK6 activity" is meant PAK6 kinase activity, binding activity, imunogenicity, or any enzymatic activity of the PAK6 protein, or the PAK6 kinase domain alone. Thus, PAK6 activity may be assayed, where appropriate, using all or a portion of the entire PAK6 molecule. For example, the PAK6 kinase domain alone may be used in

kinase, binding, immunogenicity, or other PAK6 enzymatic activities. Similarly, a modulator, inhibitor, or activator of PAK6 protein may also be a modulator, inhibitor, or activator of the PAK6 kinase domain, and modulation, inhibition or activation of PAK6 activity may be assayed by assaying the modulation, inhibition, or activation of PAK6 kinase domain activity. Also, where PAK6KD activity is assayed, portions of the PAK6 molecule in addition to the PAK6KD may be used in the assay. Thus, for example, where the present invention describes assaying modulation, inhibition, or activation of PAK6KD, instead, an assay may be performed to determine modulation, inhibition, or activation of PAK6.

[0008] Thus, in one aspect, the invention provides purified PAK6KD, and methods of purifying PAK6KD. PAK6KD may be sufficiently pure such that it may be used to prepare diffraction quality crystals. For ease of obtaining diffraction quality crystals, the purified PAK6KD may be predominantly, or entirely, of one phosphorylation state.

[0009] Thus, in one aspect, the invention provides a crystal comprising PAK6 or PAK6KD peptides in preferred crystalline form. In some embodiments of the invention the crystal is diffraction quality. The crystals of the invention include, for example, crystals of wild type PAK6KD, crystals of mutated PAK6KD, native crystals, heavy-atom derivative crystals, and crystals of PAK6KD homologs or PAK6KD mutants, such as, but not limited to, selenomethionine or selenocysteine mutants, mutants comprising conservative alterations in amino acid residues, and truncated or extended mutants.

[0010] The crystals of the invention also include co-crystals, in which crystallized PAK6KD is in association with one or more compounds, including but not limited to, cofactors, ligands, substrates, substrate analogs, inhibitors, activators, agonists, antagonists, modulators, allosteric effectors, etc., to form a crystalline co-complex. Such compounds may or may not bind a catalytic or active site of PAK6KD within the crystal. Alternatively, such compounds stably interact with another binding pocket of PAK6KD within the crystal. The co-crystals may be native co-crystals, in which the co-complex is substantially pure, or they may be heavy-atom derivative co-crystals, in which the co-complex is in association with one or more heavy-metal atoms, preferably heavy-metal atoms that promote anomalous scattering.

[0011] In other embodiments, the crystals of the invention are of sufficient quality to permit the determination of the three-dimensional X-ray diffraction structure of the crystalline polypeptide to high resolution, for example, to a resolution of better than 3Å,

or, at least 1Å and up to about 3Å, and more typically a resolution of greater than 1.5Å and up to 2Å or about 2Å, or 2.5Å or about 2.5Å.

[0012] In some embodiments, the crystals are characterized by a unit cell of a= 59.2Å+/- 2%, b= 66.7Å +/- 2%, c= 97.2Å+/- 2%, α= 90°, β= 90° , γ= 90°, and a space group of P 21 21 21.

[0013] The invention also provides methods of making the crystals of the invention. Generally, crystals of the invention are grown by dissolving substantially pure polypeptide in an aqueous buffer that includes a precipitant at a concentration just below that necessary to precipitate the polypeptide. Water is then removed by controlled evaporation to produce precipitating conditions, which are maintained until the crystal forms and the size of the crystal is appropriate.

[0014] Co-crystals of the invention are prepared by soaking a native crystal prepared according to the above method in a liquor comprising the compound of the desired co-complex. Alternatively, the co-crystals may be prepared by co-crystallizing the polypeptide in the presence of the compound according to the method discussed above.

[0015] Heavy-atom derivative crystals of the invention may be prepared by soaking native crystals or co-crystals prepared according to the above method in a liquor comprising a salt of a heavy atom or an organometallic compound. Alternatively, heavy-atom derivative crystals may be prepared by crystallizing a polypeptide comprising modified amino acids, for example, selenomethionine and/or selenocysteine residues according to the methods described above for preparing native crystals.

[0016] In yet another embodiment of the present invention, a method is provided for determining the three-dimensional structure of a PAK6KD crystal, comprising the steps of providing a crystal of the present invention; and analyzing the crystal by x-ray diffraction to determine the three-dimensional structure. Stated differently, the invention provides for the production of three-dimensional structural information (or "data") from the crystals of the invention. Such information may be in the form of structural coordinates that define the three-dimensional structure of PAK6KD in a crystal and/or co-crystal. Alternatively, the structural coordinates may define the three-dimensional structure of a portion of PAK6KD in the crystal. Non-limiting examples of portions of PAK6KD include the catalytic or active site, and a binding pocket. The structural coordinate information may include other structural information, such as vector representations of the molecular

structures coordinates, and be stored or compiled in the form of a database, optionally in electronic form.

[0017] The invention thus provides methods of producing a computer readable database comprising the three-dimensional molecular structural coordinates of binding pocket of PAK6KD, said methods comprising obtaining three-dimensional structural coordinates defining PAK6KD or a binding pocket of PAK6KD, from a crystal of PAK6KD; and introducing said structural coordinates into a computer to produce a database containing the molecular structural coordinates of PAK6KD or said binding pocket. The invention also provides databases produced by such methods.

[0018] In an alternative embodiment, the invention provides for the use of identifiers of structural information to be all or part of the information defining the three-dimensional structure of PAK6KD so that all or part of the actual structural information need not be present. For example, and without limiting the invention, identifiers which reference structural coordinates defining a three-dimensional structure, substructure or shape may be used in place of the actual coordinate information. Such reference structural information is optionally stored separately from the identifiers used to define the three-dimensional structure of PAK6KD. A non-limiting example is the use of an identifier for an alpha helix structure in place of the coordinates of the helical structure, or the use of distances and angles to represent the structure.

[0019] In another aspect, the invention provides computer machine-readable media embedded with the three-dimensional structural information obtained from the crystals of the invention, or portions or substrates thereof. The invention also provides methods for the introduction of the structural information into a computer readable medium, optionally as a computer readable database. The types of machine- or computer-readable media into which the structural information is embedded typically include magnetic tape, floppy discs, hard disc storage media, optical discs, CD-ROM, electrical storage media such as RAM or ROM, and hybrids of any of these storage media. Such media further include paper that may be read by a scanning device and converted into a three-dimensional structure with, for example, optical character recognition (OCR) software. In one example, the sheet of paper presents the molecular structure coordinates of crystalline polypeptide of the invention that are converted into, for example, a spread sheet by OCR software. The machine-readable media of the invention may further comprise additional

information that is useful for representing the three-dimensional structure, including, but not limited to, thermal parameters, chain identifiers, and connectivity information.

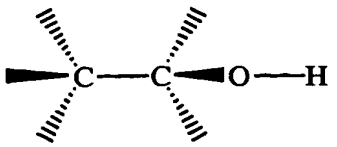
[0020] Various machine-readable media are provided in the present invention. In one aspect, a machine-readable medium is provided that is embedded with information defining a three-dimensional structural representation of any of the crystals of the present invention, or a fragment or portion thereof. The information may be in the form of molecular structure coordinates, such as, for example, those of Fig. 4. Alternatively, the information may include an identifier used to reference a particular three dimensional structure, substructure or shape. The machine-readable medium may be embedded with the molecular structure coordinates of a protein molecule comprising a PAK6KD active site, active site homolog, binding pocket or binding pocket homolog. The various machine-readable media of the present invention may also comprise data corresponding to a molecule comprising a PAK6KD binding pocket or binding pocket homolog in association with a compound or molecule bound to the protein, such as in a co-crystal.

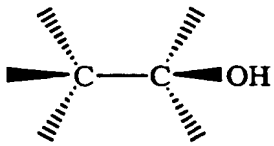
[0021] The molecular structure coordinates and machine-readable media of the invention have a variety of uses. For example, the coordinates are useful for solving the three-dimensional X-ray diffraction and/or solution structures of other proteins, including mutant PAK6KD, co-complexes comprising PAK6KD, and unrelated proteins, to high resolution. Structural information may also be used in a variety of molecular modeling and computer-based screening applications to, for example, intelligently design mutants of the crystallized PAK6KD that have altered biological activity and to computationally design and identify compounds that bind the polypeptide or a portion or fragment of the polypeptide, such as a subunit, a domain or an active site. Such compounds may be used directly or as lead compounds in pharmaceutical efforts to identify compounds that affect PAK6KD activity. Compounds that bind to the polypeptide, or to a portion or fragment thereof may be used as, for example, antimicrobial agents.

[0022] The invention thus provides methods of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of PAK6KD, said methods comprising introducing into a computer program a computer readable database comprising structural coordinates which may be used to produce a three dimensional representation of PAK6KD, generating a three-dimensional representation of a binding pocket of PAK6KD in said computer program, superimposing a three-dimensional model of at least one binding test compound on said representation of the

binding pocket, assessing whether said test compound model fits spatially into the binding pocket of PAK6KD and storing a representation of a compound that fits into the binding pocket into a computer readable database. The database used to store the representation of a compound may be the same or different from that used to store the structural coordinates of PAK6KD. The invention further provides for the electronic transmission of any structural information resulting from the practice of the invention, such as by telephonic, computer implemented, microwave mediated, and satellite mediated means as non-limiting examples.

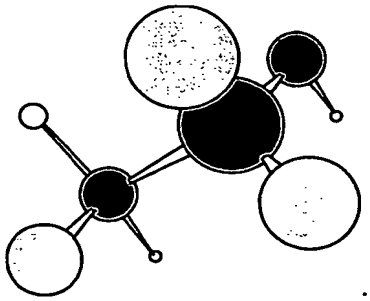
[0023] As described above, the molecular structure coordinates and/or machine-readable media associated with PAK6KD structure may also be used in the production of three-dimensional structural information (or "data") of a compound capable of binding PAK6KD. Such information may be in the form of structural coordinates that define the three-dimensional structure of a compound, optionally in combination or with reference to structural components of PAK6KD. In some embodiments, the structure coordinates of the compound are determined and presented (or represented) relative to the structure coordinates of the protein. Alternatively, identifiers of structural information are used to represent all or part of the information defining the three-dimensional structure of a compound so that all or part of the actual structural information need not be present. For example, and without limiting the invention, if the structural information of a compound includes a region defining a pyrophosphate (or pyrophosphate mimetic) moiety, the structural coordinates of pyrophosphate may be substituted by an identifier representing the structure of pyrophosphate, such as the name, chemical formula or other chemical representation. Any compound capable of binding PAK6KD may be represented by chemical name, chemical or molecular formula, chemical structure, and/or other identifying information. As a non-limiting example, the compound CH_3CH_2OH may be represented by names such as ethanol or ethyl alcohol, abbreviations such as EtOH, chemical or molecular formulas such as CH_3CH_2OH or C_2H_5OH or C_2H_6O, and/or by structural representations in two or three dimensions. Non-limiting examples of the latter include Fisher projections, electron density maps and representations, space filling models, and the following:





CH_3——CH_2–OH

H_3C——C——OH
H_2



[0024] Non-limiting examples of other identifying information include Chemical Abstract Service (CAS) Registry numbers and physical or chemical properties indicative of the compound (such as, but not limited to, NMR spectra, IR spectra, MS spectra, GC profiles, and melting point). Of course the structures of a portion of a compound (e.g. a substructure) may be similarly identified by reference to any of the above used to identify a compound as a whole.

[0025] To produce structural information of a compound capable of binding PAK6KD, the invention provides for the use of a variety of methods, including a) the superimposition of structures of known compounds on the structure of PAK6KD or a portion thereof, b) the determination of a "pharmacophore" structure which binds PAK6KD, and c) the determination of substructure(s) of compounds, wherein the substructure(s) interact with PAK6KD. The structural coordinate information may include other structural information, such as vector representations of the molecular structures coordinates, and be stored or compiled in the form of a database, optionally in electronic form. With respect to a), the invention includes the computational screening of a three-dimensional structural representation of PAK6KD or a portion thereof, or a molecule comprising a PAK6KD binding pocket or binding pocket homolog, with a plurality of chemical compounds and chemical entities. Alternatively, the present invention provides a method of identifying at least one compound that potentially binds to PAK6KD, comprising, constructing a three-

dimensional structure of a protein molecule comprising a PAK6KD binding pocket or binding pocket homolog, or constructing a three-dimensional structure of a molecule comprising a PAK6KD binding pocket, and computationally screening a plurality of compounds using the constructed structure, and identifying at least one compound that computationally binds to the structure. In one aspect, the method further comprises determining whether the compound binds PAK6KD.

[0026] With respect to b) the invention includes the computational screening of a plurality of chemical compounds to determine which compound(s), or portion(s) thereof, fit a pharmacophore determined as fitting within a PAK6KD binding pocket. Stated differently, the structures of chemical compounds may be screened to identify which compound(s), or portion(s) thereof, is encompassed by the parameters of an identified pharmacophore. As used herein, "pharmacophore" refers to the structural characteristics determined as necessary for a chemical moiety to fit or bind a PAK6KD binding pocket. A non-limiting example of a pharmacophore is a description of the electronic characteristics necessary for interaction with a binding site. These characteristics may be representations of the ground and excited state wave functions of a pharmacophore, including specification of known expansions of such functions. Representations of a pharmacophore contain the chemical moieties, and/or atoms thereof, within the pharmacophore as well as their electronic characteristics and their three dimensional arrangement in space. Other representations may also be used because different chemical moieties may have similar characteristics. A non-limiting example is seen in the case of a -SH moiety at a particular position, which has similar characteristics to a -OH moiety at the same position. Chemical moieties that may be substituted for each other within a pharmacophore are referred to as "homologous".

[0027] The present invention thus provides methods for producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of PAK6KD, said methods comprising introducing into a computer program a computer readable database comprising structural coordinates which may be used to produce a three dimensional representation of PAK6KD, determining a pharmacophore that fits within said binding pocket, computationally screening a plurality of compounds to determine which compound(s) or portion(s) thereof fit said pharmacophore, and storing a representation of said compound(s) or portion(s) thereof into a computer readable database. The database may be the same or different from that used to store the structural

coordinates of PAK6KD. Determination of a pharmacophore that fits may be performed by any means known in the art.

[0028] With respect to c) the invention includes the computational screening of a plurality of chemical compounds to determine which compounds comprise a substructure that interacts with PAK6KD. The invention thus provides methods of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of PAK6KD, said methods comprising introducing into a computer program a computer readable database comprising structural coordinates which may be used to produce a three dimensional representation of PAK6KD, determining a chemical moiety that interacts with said binding pocket, computationally screening a plurality of compounds to determine which compound(s) comprise said moiety as a substructure of said compound(s), and storing a representation of said compound(s) and/or said moiety into a computer readable database which may be the same or different from that used to store the structural coordinates of PAK6KD.

[0029] In one embodiment of the invention, the particulars of which may be used in combination with the other embodiments of the invention, a method is provided for producing structural information of a compound capable of binding PAK6KD by selecting at least one compound that potentially binds to PAK6KD. The method comprises constructing a three-dimensional structure of PAK6KD having structure coordinates selected from the group consisting of the structure coordinates of the crystals of the present invention, the structure coordinates of Fig. 4, and the structure coordinates of a protein having a root mean square deviation of the alpha carbon atoms of up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1Å, preferably up to about 0.75Å, preferably up to about 0.5Å, and preferably up to about 0.25Å, when compared to the structure coordinates of Fig. 4, or a portion thereof, or constructing a three-dimensional structure of a molecule comprising a PAK6KD binding pocket or binding pocket homolog; and selecting at least one compound which potentially binds PAK6KD; wherein the selecting is performed with the aid of the constructed structure of PAK6KD.

[0030] It is anticipated that in some cases, upon binding a compound, the conformation of the protein may be altered. Useful compounds may bind to this altered conformational form. Thus, included within the scope of the present invention are methods of producing structural information of a compound capable of binding PAK6KD by selecting compounds that potentially bind to a PAK6KD molecule or homolog where the molecule

or homolog comprises an amino acid sequence that is at least 50%, preferably at least 60%, more preferably at least 70%, more preferably at least 80%, and more preferably at least 90% identical to the amino acid sequence of Fig. 2, using, for example, a PSI BLAST search, such as, but not limited to version 2.2.2 (Altschul, S.F., et al., Nuc. Acids Rec. 25:3389-3402, 1997). Preferably at least 50%, more preferably at least 70% of the sequence is aligned in this analysis and where at least 50%, more preferably 60%, more preferably 70%, more preferably 80%, and most preferably 90% of the amino acids of the molecule or homolog have structure coordinates selected from the group consisting of the structure coordinates of the crystals of the present invention, the structure coordinates of Fig. 4, and the structure coordinates of a protein having a root mean square deviation of the alpha carbon atoms of up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1Å, preferably up to about 0.75Å, preferably up to about 0.5Å, and preferably up to about 0.25Å, when compared to the structure coordinates of Fig. 4, or a portion thereof, or constructing a three dimensional structure of a molecule comprising a PAK6 binding pocket or binding pocket homolog; and selecting at least one compound which potentially binds PAK6; wherein the selecting is performed with the aid of the constructed structure. The selected compounds thus provide information concerning the structure of compounds that bind PAK6.

[0031] Once produced, structural information of a compound capable of binding PAK6 may be stored in machine-readable form as described above for PAK6 structural information.

[0032] In yet another aspect of the present invention, a method is provided of identifying a modulator of PAK6 by rational drug design, comprising; designing a potential modulator of PAK6 that forms covalent or non-covalent bonds with amino acids in a binding pocket of PAK6 based on the molecular structure coordinates of the crystals of the present invention, or based on the molecular structure coordinates of a molecule comprising a PAK6 binding pocket or binding pocket homolog; synthesizing the modulator; and determining whether the potential modulator affects the activity of PAK6. The binding pocket may, for example, comprise the active site of PAK6. The binding pocket may instead comprise an allosteric binding pocket of PAK6. A modulator may be, for example, an inhibitor, an activator, or an allosteric modulator of PAK6.

[0033] Other methods of designing modulators of PAK6 include, for example, a method for identifying a modulator of PAK6 activity comprising: providing a computer

modeling program with a three dimensional conformation for a molecule that comprises a binding pocket of PAK6, or binding pocket homolog; providing a said computer modeling program with a set of structure coordinates of a chemical entity; using said computer modeling program to evaluate the potential binding or interfering interactions between the chemical entity and said binding pocket, or binding pocket homolog; and determining whether said chemical entity potentially binds to or interferes with said molecule; wherein binding to the molecule is indicative of potential modulation, including, for example, inhibition of PAK6 activity.

[0034] In another embodiment, a method is provided for designing a modulator of PAK6 activity comprising: providing a computer modeling program with a set of structure coordinates, or a three dimensional conformation derived therefrom, for a molecule that comprises a binding pocket of PAK6, or binding pocket homolog; providing a said computer modeling program with a set of structure coordinates, or a three dimensional conformation derived therefrom, of a chemical entity; using said computer modeling program to evaluate the potential binding or interfering interactions between the chemical entity and said binding pocket, or binding pocket homolog; computationally modifying the structure coordinates or three dimensional conformation of said chemical entity; and determining whether said modified chemical entity potentially binds to or interferes with said molecule; wherein binding to the molecule is indicative of potential modulation of PAK6 activity.

[0035] In other aspects, determining whether the chemical entity potentially binds to said molecule comprises performing a fitting operation between the chemical entity and a binding pocket, or binding pocket homolog, of the molecule or molecular complex; and computationally analyzing the results of the fitting operation to quantify the association between, or the interference with, the chemical entity and the binding pocket, or binding pocket homolog. In a further embodiment, the method further comprises screening a library of chemical entities.

[0036] The PAK6 modulator may also be designed *de novo*. Thus, the present invention also provides a method for designing a modulator of PAK6, comprising: providing a computer modeling program with a set of structure coordinates, or a three dimensional conformation derived therefrom, for a molecule that comprises a binding pocket having the structure coordinates of the binding pocket of PAK6, or a binding pocket homolog; computationally building a chemical entity represented by set of

structure coordinates; and determining whether the chemical entity is a modulator expected to bind to or interfere with the molecule wherein binding to the molecule is indicative of potential modulation of PAK6 activity. In other embodiments, determining whether the chemical entity potentially binds to said molecule comprises performing a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex, or a binding pocket homolog; and computationally analyzing the results of the fitting operation to quantify the association between, or the interference with, the chemical entity and the binding pocket, or a binding pocket homolog.

[0037] In yet other embodiments, once a modulator is computationally designed or identified, the potential modulator may be supplied or synthesized, then assayed to determine whether it inhibits PAK6 activity. The molecular structure coordinates and/or machine-readable media associated with the PAK6 structure and/or a compound capable of binding PAK6KD may be used in the production of compounds capable of binding PAK6. Methods for the production of such compounds include the preparation of an initial compound containing chemical groups most likely to bind or interact with residues of PAK6KD based upon the molecular structure coordinates of PAK6KD and/or a compound capable of binding it. Such an initial compound may also be viewed as a scaffold comprising one or more reactive moieties (chemical groups) that are capable of binding or interacting with PAK6 residues. The initial compound may be further optimized for binding to PAK6 by introduction of additional chemical groups for increased interactions with PAK6KD residues. An initial compound may thus comprise reactive groups which may be used to introduce one or more additional chemical groups into the compound. The introduction of additional groups may also be at positions of an initial compound that do not result in interactions with PAK6 residues, but rather improve other characteristics of the compound, such as, but not limited to, stability against degradation, handling or storage, solubility in hydrophilic and hydrophobic environments, and overall charge dynamics of the compound.

[0038] The present invention also provides modulators of PAK6 activity identified, designed, or made according to any of the methods of the present invention, as well as pharmaceutical compositions comprising such modulators. Pharmaceutical compositions may be in the form of a salt, and may further comprise a pharmaceutically acceptable carrier. A modulator may be identified or confirmed as an activator or inhibitor by contacting a protein that comprises a PAK6 active site or binding pocket with said

modulator and determining whether it activates or inhibits the activity of the protein. The activity may be PAK6 activity. A naturally occurring PAK6 protein may also be used in such methods.

[0039] Also provided in the present invention is a method of modulating PAK6 activity comprising contacting PAK6 with a modulator designed or identified according to the present invention. Methods include methods of treating a disease or condition associated with inappropriate PAK6 activity comprising the method of administering by, for example, contacting cells of an individual with a PAK6 modulator designed or identified according to the present invention. The term "inappropriate activity" refers to PAK6 activity that is higher or lower than that in normal cells.

[0040] The molecular structure coordinates and/or machine-readable media of the invention may also be used in identification of active sites and binding pockets of PAK6KD. Methods for the identification of such sites and pockets are known in the art. The techniques include the use of sequence comparisons to identify regions of homology or conserved substitutions which define conserved structure among different forms of PAK6KD. The techniques may also include comparisons of structure with other proteins with the same activities as PAK6 to identify the structural components (e.g. amino acid residues and/or their arrangement in three dimensions) of the active sites and binding pockets.

[0041] In another embodiment of the present invention, a method is provided for producing a mutant of PAK6, having an altered property relative to PAK6, comprising, a) constructing a three-dimensional structure of PAK6KD having structure coordinates selected from the group consisting of the structure coordinates of the crystals of the present invention, the structure coordinates of Fig. 4, and the structure coordinates of a protein having a root mean square deviation of the alpha carbon atoms of the protein of up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1Å, preferably up to about 0.75Å, preferably up to about 0.5Å, and preferably up to about 0.25Å, when compared to the structure coordinates of Fig. 4; b) using modeling methods to identify in the three-dimensional structure at least one structural part of the PAK6KD molecule wherein an alteration in the structural part is predicted to result in the altered property; c) providing a nucleic acid molecule having a modified sequence that encodes a deletion, insertion, or substitution of one or more amino acids at a position corresponding to the structural part; and d) expressing the nucleic acid molecule to produce the mutant; wherein

the mutant has at least one altered property relative to the parent. The mutant may, for example, have altered PAK6 activity. The altered PAK6 activity may be, for example, altered binding activity, altered enzymatic activity, and altered immunogenicity, such as, for example, where an epitope of the protein is altered because of the mutation. The mutation that alters the epitope may be, for example, within the region of the protein that comprises the epitope. Or, the mutation may be, for example, at a site outside of the epitope region, yet causes a conformational change in the epitope region. Those of ordinary skill in the art will recognize that the region that contains the epitope may comprise either contiguous or non-contiguous amino acids.

[0042] Also provided in the present invention is a method for obtaining structural information about a molecule or a molecular complex of unknown structure comprising: crystallizing the molecule or molecular complex; generating an x-ray diffraction pattern from the crystallized molecule or molecular complex; and using a molecular replacement method to interpret the structure of said molecule; wherein said molecular replacement method uses the structure coordinates of Fig. 4, or structure coordinates having a root mean square deviation for the alpha-carbon atoms of said structure coordinates of up to about 2.0Å, preferably up to about 1.75Å, preferably up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1.0Å, preferably up to about 0.75Å, the structure coordinates of the binding pocket of Fig. 4, or a binding pocket homolog. The coordinates of the resulting structure are stored in a computer readable database as described herein.

[0043] In another aspect of the invention, a method is provided of using the PAK6KD structure coordinates, or the PAK6KD binding site, active site, or accessory binding site structure coordinates as an anti-target in rational drug design. When designing compounds that modulate a protein target's activity, it is often desirable to increase specificity for the target and reduce side effects. The protein structure information is useful to design compounds that do not bind to, interact with, or modulate the activity of the protein. Thus, one aspect of the present invention comprises the use of anti-target structures to assist in selecting a compound that modulates the target, but does not modulate PAK6, or does not modulate PAK6 in sufficient amount to cause a detrimental side affect. The target may, for example, be another kinase. The target may be another PAK kinase.

[0044] Thus, in one aspect of the invention, a method is provided of identifying a compound that modulates the activity of a target protein, comprising: a) introducing into a computer program information derived from structural coordinates defining an active site

conformation of a target protein molecule based upon three-dimensional structure determination, wherein said program utilizes or displays the three-dimensional structure thereof; b) generating a three-dimensional representation of the active site cavity of said target protein in said computer program; c) superimposing a model of a test compound on the model of said active site of said target protein; d) assessing whether said test compound model fits spatially into the active site of said target protein; e) generating a three-dimensional representation of a binding pocket of a PAK6KD protein in a computer program; f) superimposing a model of said test compound on the model of said binding pocket of said PAK6KD protein; and g) assessing whether said test compound model fits spatially into said binding pocket of said PAK6KD protein.

[0045] The binding pocket of the PAK6KD protein may be, for example, an active site or an accessory binding site. Said target protein may be a kinase. The test compound model may or may not fit spatially into the binding pocket of said PAK6KD protein. The method may further comprise performing a fitting operation to computationally analyze the association between the test compound and the PAK6KD protein. The test compound may bind with greater efficiency to the target protein than to the PAK6KD protein; the test compound likely does not bind to the PAK6KD protein.

[0046] In yet another aspect of the invention, a method is provided for homology modeling of a PAK6KD homolog comprising: aligning the amino acid sequence of a PAK6KD homolog with an amino acid sequence of PAK6KD; incorporating the sequence of the PAK6KD homolog into a model of the structure of PAK6KD, wherein said model has the same structure coordinates as the structure coordinates of Fig. 4, or wherein the structure coordinates of said model's alpha-carbon atoms have a root mean square deviation from the structure coordinates of Fig. 4 of up to about 2.0Å, preferably up to about 1.75Å, preferably up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1.0Å, and preferably up to about 0.75Å, to yield a preliminary model of said homolog; subjecting the preliminary model to energy minimization to yield an energy minimized model; and remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of said homolog.

[0047] The invention also provides PAK6KD in crystalline form, as well as a computer or machine readable medium containing information that reflects the three dimensional structure of such crystals and/or compounds that interact with them. Also provided is a method of producing a computer readable database containing the three-dimensional

molecular structure coordinates of a compound capable of binding the active site or binding pocket of a PAK6KD but not another protein molecule. Such a method comprises a) introducing into a computer program information concerning the structure of PAK6KD; b) generating a three-dimensional representation of the active site or binding pocket of PAK6KD in said computer program; c) superimposing a three-dimensional model of at least one binding test compound on said representation of the active site or binding pocket; d) assessing whether said test compound model fits spatially into the active site or binding pocket of PAK6KD; e) assessing whether a compound that fits will fit a three-dimensional model of another protein, the structural coordinates of which are also introduced into said computer program and used to generate a three-dimensional representation of the other protein; and f) storing the three-dimensional molecular structure coordinates of a model that does not fit the other protein into a computer readable database. An alternative form of such a method produces a computer readable database containing the three-dimensional molecular structural coordinates of a compound capable of specifically binding the active site or binding pocket of PAK6KD, said method comprising introducing into a computer program a computer readable database containing the structural coordinates of PAK6KD, generating a three-dimensional representation of the active site or binding pocket of PAK6KD in said computer program, superimposing a three-dimensional model of at least one binding test compound on said representation of the active site or binding pocket, assessing whether said test compound model fits spatially into the active site or binding pocket of PAK6KD, assessing whether a compound that fits will fit a three-dimensional model of another protein, the structural coordinates of which are also introduced into said computer program and used to generate a three-dimensional representation of the other protein, and storing the three-dimensional molecular structural coordinates of a model that does not fit the other protein into a computer readable database. Conversely, such methods may be used to determine that compounds identified as binding other proteins do not bind PAK6KD. Thus, such methods may use PAK6KD as an anti-target, to identify compounds that do not bind PAK6KD.

[0048] The invention also provides methods comprising the production of a co-crystal of a compound and PAK6KD. Such co-crystals may be used in a variety of ways, including the determination of structural coordinates of the compound and/or PAK6KD, or a binding pocket thereof, in the co-crystal. Such coordinates may be introduced and/or stored in a computer readable database in accordance with the present invention for further

use. The invention thus provides methods of producing a computer readable database comprising a representation of a binding pocket of PAK6KD in a co-crystal with a compound, said methods comprising preparing a binding test compound represented in a computer readable database produced by any method described herein, forming a co-crystal of said compound with a protein comprising a binding pocket of PAK6KD, obtaining the structural coordinates of said binding pocket in said co-crystal, and introducing the structural coordinates of said binding pocket or said co-crystal into a computer-readable database. The invention further provides for a combination of such methods with rational compound design by providing methods of producing a computer readable database comprising a representation of a binding pocket of PAK6KD in a co-crystal with a compound rationally designed to be capable of binding said binding pocket, said methods comprising preparing a binding test compound represented in a computer readable database produced by any method described herein, forming a co-crystal of said compound with a protein comprising a binding pocket of PAK6KD, obtaining the structural coordinates of said binding pocket in said co-crystal, and introducing the structural coordinates of said binding pocket or said co-crystal into a computer-readable database.

[0049] The invention is illustrated by way of the present application, including working examples demonstrating the purification and the crystallization of PAK6KD, the characterization of crystals, the collection of diffraction data, and the determination and analysis of the three-dimensional structure of PAK6KD.

BRIEF DESCRIPTION OF THE FIGURES

[0050] FIG. 1 provides a ribbon diagram of the structure of PAK6KD.

[0051] FIG. 2 provides the predicted amino acid sequence of the PAK6KD expressed protein used to obtain the crystals and structural coordinates of the present invention. Note that this amino acid sequence may comprise amino acids encoded by the ORF, as well as other amino acids encoded by the expression vector. Further information regarding sequence changes, if any, may be found in the examples.

[0052] FIG. 3 provides a ribbon diagram of the structure of PAK6KD.

[0053] FIG. 4 (A-RR) provides the molecular structure coordinates of PAK6KD.

[0054] The following abbreviations are used in Figure 4.

[0055] "Atom Type" and "Atom" refer to the individual atom whose coordinates are provided, with and without indicating the position of the atom in the amino acid residue, respectively. The first letter in the column refers to the element.

[0056] HETATM refers to atomic coordinates within non-standard HET groups, such as prosthetic groups, inhibitors, solvent molecules, and ions for which coordinates are supplied. HETATMS include residues that are a) not one of the standard amino acids, including, for example, SeMet and SeCys, b) not one of the nucleic acids (C, G, A, T, U, and I), c) not one of the modified versions of nucleic acids (+C, +G, +A, +T, +U, and +I), and d) not an unknown amino acid or nucleic acid where UNK is used to indicate the unknown residue name.

[0057] "Residue" refers to the amino acid residue.

[0058] "#" refers to the residue number, starting from the N-terminal amino acid. The number designations of each amino acid residues reflect the position predicted in the expressed protein, including the His tag and the initial methionine.

[0059] "X, Y and Z" provide the Cartesian coordinates of the atom.

[0060] "B" is a thermal factor that measures movement of the atom around its atomic center.

[0061] "OCC" refers to occupancy, and represents the percentage of time the atom type occupies the particular coordinate. OCC values range from 0 to 1, with 1 being 100%.

[0062] Structure coordinates for PAK6KD according to Figure 4 may be modified by mathematical manipulation. Such manipulations include, but are not limited to, crystallographic permutations of the raw structure coordinates, fractionalization of the raw structure coordinates, integer additions or subtractions to sets of the raw structure coordinates, inversion of the raw structure coordinates, and any combination of the above.

Abbreviations

[0063] The amino acid notations used herein for the twenty genetically encoded amino acids are:

Amino Acid	One-Letter Symbol	Three-Letter Symbol
Alanine	A	Ala
Arginine	R	Arg

Asparagine	N	Asn
Aspartic acid	D	Asp
Cysteine	C	Cys
Glutamine	Q	Gln
Glutamic acid	E	Glu
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Leucine	L	Leu
Lysine	K	Lys
Methionine	M	Met
Phenylalanine	F	Phe
Proline	P	Pro
Serine	S	Ser
Threonine	T	Thr
Tryptophan	W	Trp
Tyrosine	Y	Tyr
Valine	V	Val

[0064] As used herein, unless specifically delineated otherwise, the three-letter amino acid abbreviations designate amino acids in the L-configuration. Amino acids in the D-configuration are preceded with a "D-." For example, Arg designates L-arginine and D-Arg designates D-arginine. Likewise, the capital one-letter abbreviations refer to amino acids in the L-configuration. Lower-case one-letter abbreviations designate amino acids in the D-configuration. For example, "R" designates L-arginine and "r" designates D-arginine.

[0065] Unless noted otherwise, when polypeptide sequences are presented as a series of one-letter and/or three-letter abbreviations, the sequences are presented in the N→C direction, in accordance with common practice.

Definitions

[0066] As used herein, the following terms shall have the following meanings:

[0067] "Genetically Encoded Amino Acid" refers to the twenty amino acids that are defined by genetic codons. The genetically encoded amino acids are glycine and the L-isomers of alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, arginine and lysine.

[0068] "Non-Genetically Encoded Amino Acid" refers to amino acids that are not defined by genetic codons. Non-genetically encoded amino acids include derivatives or analogs of the genetically-encoded amino acids that are capable of being enzymatically incorporated into nascent polypeptides using conventional expression systems, such as selenomethionine (SeMet) and selenocysteine (SeCys); isomers of the genetically-encoded amino acids that are not capable of being enzymatically incorporated into nascent polypeptides using conventional expression systems, such as D-isomers of the genetically-encoded amino acids; L- and D-isomers of naturally occurring α-amino acids that are not defined by genetic codons, such as α-aminoisobutyric acid (Aib); L- and D-isomers of synthetic α-amino acids that are not defined by genetic codons; and other amino acids such as β-amino acids,γ-amino acids, etc. In addition to the D-isomers of the genetically-encoded amino acids, common non-genetically encoded amino acids include, but are not limited to norleucine (Nle), penicillamine (Pen), N-methylvaline (MeVal), homocysteine (hCys), homoserine (hSer), 2,3-diaminobutyric acid (Dab) and ornithine (Orn). Additional exemplary non-genetically encoded amino acids are found, for example, in *Practical Handbook of Biochemistry and Molecular Biology*, Fasman, Ed., CRC Press, Inc., Boca Raton, FL, pp. 3-76, 1989, and the various references cited therein.

[0069] "Hydrophilic Amino Acid" refers to an amino acid having a side chain exhibiting a hydrophobicity of up to about zero according to the normalized consensus hydrophobicity scale of Eisenberg *et al.*, J. Mol. Biol. 179:125-42, 1984. Genetically encoded hydrophilic amino acids include Thr (T), Ser (S), His (H), Glu (E), Asn (N), Gln (Q), Asp (D), Lys (K) and Arg (R). Non-genetically encoded hydrophilic amino acids include the D-isomers of the above-listed genetically-encoded amino acids, ornithine (Orn), 2,3-diaminobutyric acid (Dab) and homoserine (hSer).

[0070] "Acidic Amino Acid" refers to a hydrophilic amino acid having a side chain pK value of up to about 7 under physiological conditions. Acidic amino acids typically have negatively charged side chains at physiological pH due to loss of a hydrogen ion.

Genetically encoded acidic amino acids include Glu (E) and Asp (D). Non-genetically encoded acidic amino acids include D-Glu (e) and D-Asp (d).

[0071] "Basic Amino Acid" refers to a hydrophilic amino acid having a side chain pK value of greater than 7 under physiological conditions. Basic amino acids typically have positively charged side chains at physiological pH due to association with hydronium ion. Genetically encoded basic amino acids include His (H), Arg (R) and Lys (K). Non-genetically encoded basic amino acids include the D-isomers of the above-listed genetically-encoded amino acids, ornithine (Orn) and 2,3-diaminobutyric acid (Dab).

[0072] "Polar Amino Acid" refers to a hydrophilic amino acid having a side chain that is uncharged at physiological pH, but which comprises at least one covalent bond in which the pair of electrons shared in common by two atoms is held more closely by one of the atoms. Genetically encoded polar amino acids include Asn (N), Gln (Q), Ser (S), and Thr (T). Non-genetically encoded polar amino acids include the D-isomers of the above-listed genetically-encoded amino acids and homoserine (hSer).

[0073] "Hydrophobic Amino Acid" refers to an amino acid having a side chain exhibiting a hydrophobicity of greater than zero according to the normalized consensus hydrophobicity scale of Eisenberg *et al.*, J. Mol. Biol. 179:125-42, 1984. Genetically encoded hydrophobic amino acids include Pro (P), Ile (I), Phe (F), Val (V), Leu (L), Trp (W), Met (M), Ala (A), Gly (G) and Tyr (Y). Non-genetically encoded hydrophobic amino acids include the D-isomers of the above-listed genetically-encoded amino acids, norleucine (Nle) and N-methyl valine (MeVal).

[0074] "Aromatic Amino Acid" refers to a hydrophobic amino acid having a side chain comprising at least one aromatic or heteroaromatic ring. The aromatic or heteroaromatic ring may contain one or more substituents such as -OH, -SH, -CN, -F, -Cl, -Br, -I, $-NO_2$, -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, $-C(O)NH_2$, -C(O)NHR, -C(O)NRR and the like where each R is independently (C_1-C_6) alkyl, (C_1-C_6) alkenyl, or (C_1-C_6) alkynyl. Genetically encoded aromatic amino acids include Phe (F), Tyr (Y), Trp (W) and His (H). Non-genetically encoded aromatic amino acids include the D-isomers of the above-listed genetically-encoded amino acids.

[0075] "Apolar Amino Acid" refers to a hydrophobic amino acid having a side chain that is uncharged at physiological pH and which has bonds in which the pair of electrons shared in common by two atoms is generally held equally by each of the two atoms (*i.e.*, the side chain is not polar). Genetically encoded apolar amino acids include Leu (L), Val

(V), Ile (I), Met (M), Gly (G) and Ala (A). Non-genetically encoded apolar amino acids include the D-isomers of the above-listed genetically-encoded amino acids, norleucine (Nle) and N-methyl valine (MeVal).

[0076] "Aliphatic Amino Acid" refers to a hydrophobic amino acid having an aliphatic hydrocarbon side chain. Genetically encoded aliphatic amino acids include Ala (A), Val (V), Leu (L) and Ile (I). Non-genetically encoded aliphatic amino acids include the D-isomers of the above-listed genetically-encoded amino acids, norleucine (Nle) and N-methyl valine (MeVal).

[0077] "Helix-Breaking Amino Acid" refers to those amino acids that have a propensity to disrupt the structure of α-helices when contained at internal positions within the helix. Amino acid residues exhibiting helix-breaking properties are well-known in the art (*see, e.g.*, Chou & Fasman, *Ann. Rev. Biochem.* 47:251-76, 1978) and include Pro (P), D-Pro (p), Gly (G) and potentially all D-amino acids (when contained in an L-polypeptide; conversely, L-amino acids disrupt helical structure when contained in a D-polypeptide).

[0078] "Cysteine-like Amino Acid" refers to an amino acid having a side chain capable of participating in a disulfide linkage. Thus, cysteine-like amino acids generally have a side chain containing at least one thiol (-SH) group. Cysteine-like amino acids are unusual in that they can form disulfide bridges with other cysteine-like amino acids. The ability of Cys (C) residues and other cysteine-like amino acids to exist in a polypeptide in either the reduced free -SH or oxidized disulfide-bridged form affects whether they contribute net hydrophobic or hydrophilic character to a polypeptide. Thus, while Cys (C) exhibits a hydrophobicity of 0.29 according to the consensus scale of Eisenberg (Eisenberg, 1984, *supra*), it is to be understood that for purposes of the present invention Cys (C) is categorized as a polar hydrophilic amino acid, notwithstanding the general classifications defined above. Other cysteine-like amino acids are similarly categorized as polar hydrophilic amino acids. Typical cysteine-like residues include, for example, penicillamine (Pen), homocysteine (hCys), etc.

[0079] As will be appreciated by those of skill in the art, the above-defined classes or categories are not mutually exclusive. Thus, amino acids having side chains exhibiting two or more physical-chemical properties may be included in multiple categories. For example, amino acid side chains having aromatic groups that are further substituted with polar substituents, such as Tyr (Y), may exhibit both aromatic hydrophobic properties and polar or hydrophilic properties, and could therefore be included in both the aromatic and

polar categories. Typically, amino acids will be categorized in the class or classes that most closely define their net physical-chemical properties. The appropriate categorization of any amino acid will be apparent to those of skill in the art.

[0080] Other amino acid residues not specifically mentioned herein may be readily categorized based on their observed physical and chemical properties in light of the definitions provided herein.

[0081] "Wild-type PAK6KD" refers to a polypeptide having an amino acid sequence that corresponds to the amino acid sequence of a naturally-occurring PAK6KD, and wherein said polypeptide, when compared to PAK6KD, has an rmsd of its backbone atoms of less than 2Å.

[0082] "Homo sapiens PAK6KD" refers to a polypeptide having an amino acid sequence that corresponds identically to the wild-type PAK6KD from Homo sapiens.

[0083] By "or" is meant one, or another member of a group, or more than one member. For example, A, B, or C, may indicate any of the following: A alone; B alone; C alone; A and B; B and C; A and C; A, B, and C.

[0084] "Association" refers to the status of two or more molecules that are in close proximity to each other. The two molecules may be associated non-covalently, for example, by hydrogen-bonding, van der Waals, electrostatic or hydrophobic interactions, or covalently.

[0085] "Co-Complex" refers to a polypeptide in association with one or more compounds. The association may be, for example, covalent or non-covalent. A "PAK6KD co-complex" refers to PAK6KD, or a functional subunit or fragment thereof, in association with one or more compounds. Such compounds include, by way of example and not limitation, cofactors, ligands, substrates, substrate analogues, inhibitors, allosteric affecters, etc. Lead compounds for designing PAK6 inhibitors include, but are not restricted to, ATP; β-amido ATP; AMP-PNP, staurosporine, and derivatives and analogs thereof. A co-complex may also refer to a computer represented, or *in silica* generated association between a peptide and a compound. An "unliganded" form of a protein structure, or structural coordinates thereof, refers to the coordinates of the native form of a protein structure, or the apostructure, not a co-complex. A "liganded" form refers to the coordinates of a protein or peptide that is part of a co-complex. Unliganded forms include peptides and proteins associated with various ions, such as manganese, zinc, and magnesium, as well as with water. Ligands include natural substrates, non-natural

substrates, inhibitors, substrate analogs, agonists or antagonists, proteins, co-factors small molecules, test compounds, and fragments of test compounds, as well as, optionally, in addition, various ions or water.

[0086] "Mutant" refers to a polypeptide characterized by an amino acid sequence that differs from the wild-type sequence by the substitution of at least one amino acid residue of the wild-type sequence with a different amino acid residue and/or by the addition and/or deletion of one or more amino acid residues to or from the wild-type sequence. The additions and/or deletions may be from an internal region of the wild-type sequence and/or at either or both of the N- or C-termini. A mutant polypeptide may have substantially the same three-dimensional structure as the corresponding wild-type polypeptide. A mutant may have, but need not have, PAK6 activity. A mutant may display biological activity that is substantially similar to that of the wild-type PAK6KD. By "substantially similar biological activity" is meant that the mutant displays biological activity that is within 1% to 10,000% of the biological activity of the wild-type polypeptide, for example, within 25% to 5,000%, and, for example, within 50% to 500%, or 75% to 200% of the biological activity of the wild-type polypeptide, using assays known to those of ordinary skill in the art for that particular class of polypeptides. Mutants may also decrease or eliminate PAK6KD activity. Mutants may be synthesized according to any method known to those skilled in the art, including, but not limited to, those methods of expressing PAK6KD molecules described herein.

[0087] "Active Site" refers to a site in PAK6KD that associates with the substrate for PAK6 activity. This site may include, for example, residues involved in catalysis, as well as residues involved in binding a substrate. Inibitors may bind to the residues of the active site. In PAK6KD, the active site includes one or more of the following amino acid residues: Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

[0088] Preferably, the active site comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544, preferably the active site further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530. Preferably the active site further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 .

Amino acid residue numbers presented herein refer to the sequence of wild type full length PAK6. Those of ordinary skill in the art may easily determine the residue numbers corresponding to any modified form of PAK6 using standard alignment protocols, including, for example, alignments done by hand.

[0089] "Binding Pocket" refers to a region in PAK6 which associates with a ligand such as a natural substrate, non-natural substrate, inhibitor, substrate analog, agonist or antagonist, protein, co-factor or small molecule, as well as, optionally, in addition, various ions or water, and/or has an internal cavity sufficient to bind a small molecule and may be used as a target for binding drugs. The term includes the active site but is not limited thereby.

[0090] "Accessory Binding Pocket" refers to a binding pocket in PAK6KD other than that of the "active site."

[0091] "Conservative Mutant" refers to a mutant in which at least one amino acid residue from the wild-type sequence is substituted with a different amino acid residue that has similar physical and chemical properties, *i.e.*, an amino acid residue that is a member of the same class or category, as defined above. For example, a conservative mutant may be a polypeptide that differs in amino acid sequence from the wild-type sequence by the substitution of a specific aromatic Phe (F) residue with an aromatic Tyr (Y) or Trp (W) residue.

[0092] "Non-Conservative Mutant" refers to a mutant in which at least one amino acid residue from the wild-type sequence is substituted with a different amino acid residue that has dissimilar physical and/or chemical properties, *i.e.*, an amino acid residue that is a member of a different class or category, as defined above. For example, a non-conservative mutant may be a polypeptide that differs in amino acid sequence from the wild-type sequence by the substitution of an acidic Glu (E) residue with a basic Arg (R), Lys (K) or Orn residue.

[0093] "Deletion Mutant" refers to a mutant having an amino acid sequence that differs from the wild-type sequence by the deletion of one or more amino acid residues from the wild-type sequence. The residues may be deleted from internal regions of the wild-type sequence and/or from one or both termini.

[0094] "Truncated Mutant" refers to a deletion mutant in which the deleted residues are from the N- and/or C-terminus of the wild-type sequence.

[0095] "Extended Mutant" refers to a mutant in which additional residues are added to the N- and/or C-terminus of the wild-type sequence.

[0096] "Methionine mutant" refers to (1) a mutant in which at least one methionine residue of the wild-type sequence is replaced with another residue, such as with an aliphatic residue, such as an Ala (A), Leu (L), or Ile (I) residue; or (2) a mutant in which a non-methionine residue, such as an aliphatic residue, such as an Ala (A), Leu (L) or Ile (I) residue, of the wild-type sequence is replaced with a methionine residue.

[0097] "Selenomethionine mutant" refers to (1) a mutant which includes at least one selenomethionine (SeMet) residue, typically by substitution of a Met residue of the wild-type sequence with a SeMet residue, or by addition of one or more SeMet residues at one or both termini, or (2) a methionine mutant in which at least one Met residue is substituted with a SeMet residue. In some embodiments, each Met residue is substituted with a SeMet residue.

[0098] "Cysteine mutant" refers to a mutant in which at least one cysteine residue of the wild-type sequence is replaced with another residue, such as with a Ser (S) residue.

[0100] "Serine mutant" refers to a mutant in which at least one serine residue of the wild-type sequence is replaced with another residue, such as with a cysteine residue.

[0101] "Selenocysteine mutant" refers to (1) a mutant which includes at least one selenocysteine (SeCys) residue, typically by substitution of a Cys residue of the wild-type sequence with a SeCys residue, or by addition of one or more SeCys residues at one or both termini, or (2) a cysteine mutant in which at least one Cys residue is substituted with a SeCys residue. In some embodiments, SeCys mutants are those in which each Cys residue is substituted with a SeCys residue.

[0102] "Homolog" refers to a polypeptide having at least 30%, preferably at least 40%, preferably at least 50%, preferably at least 60%, preferably at least 70%, more preferably at least 80%, and most preferably at least 90% amino acid sequence identity or having a BLAST E-value of 1 x 10^{-6} over at least 100 amino acids (Altschul et al., *Nucleic Acids Res.*, 25:3389-402, 1997) with PAK6KD or any functional domain of PAK6KD.

[0103] "Crystal" refers to a composition comprising a polypeptide in crystalline form. The term "crystal" includes native crystals, heavy-atom derivative crystals and co-crystals, as defined herein.

[0104] "Native Crystal" refers to a crystal wherein the polypeptide is substantially pure. As used herein, native crystals do not include crystals of polypeptides comprising amino

acids that are modified with heavy atoms, such as crystals of selenomethionine mutants, selenocysteine mutants, etc.

[0105] "Heavy-atom Derivative Crystal" refers to a crystal wherein the polypeptide is in association with one or more heavy-metal atoms. As used herein, heavy-atom derivative crystals include native crystals into which a heavy metal atom is soaked, as well as crystals of selenomethionine mutants and selenocysteine mutants.

[0106] "Co-Crystal" refers to a crystalline form of a co-complex.

[0107] "Apo-crystal" refers to a crystal wherein the polypeptide is substantially pure and substantially free of compounds that might form a co-complex with the polypeptide such as cofactors, ligands, substrates, substrate analogues, inhibitors, allosteric affecters, etc.

[0108] "Diffraction Quality Crystal" refers to a crystal that is well-ordered and of a sufficient size, *i.e.*, at least 10μm, at least 50μm, or at least 100μm in its smallest dimension such that it produces measurable diffraction to at least 3Å resolution, preferably to at least 2Å resolution, and most preferably to at least 1.5Å resolution or lower. Diffraction quality crystals include native crystals, heavy-atom derivative crystals, and co-crystals.

[0109] "Unit Cell" refers to the smallest and simplest volume element (*i.e.*, parallelepiped-shaped block) of a crystal that is completely representative of the unit or pattern of the crystal, such that the entire crystal may be generated by translation of the unit cell. The dimensions of the unit cell are defined by six numbers: dimensions a, b and c and the angles are defined as α, β, and γ (Blundell *et al.*, Protein Crystallography, 83-84, Academic Press. 1976). A crystal is an efficiently packed array of many unit cells.

[0110] "Triclinic Unit Cell" refers to a unit cell in which $a \neq b \neq c$ and $\alpha \neq \beta \neq \gamma$.

[0111] "Monoclinic Unit Cell" refers to a unit cell in which $a \neq b \neq c$; $\alpha = \gamma = 90°$; and $\beta > 90°$.

[0112] "Hexagonal Unit Cell" refers to a unit cell in which $a = b \neq c$; $\alpha = \beta = 90°$; and $\gamma = 120°$.

[0113] "Orthorhombic Unit Cell" refers to a unit cell in which $a \neq b \neq c$; and $\alpha = \beta = \gamma = 90°$.

[0114] "Tetragonal Unit Cell" refers to a unit cell in which $a = b \neq c$; and $\alpha = \beta = \gamma = 90°$.

[0115] "Trigonal/Rhombohedral Unit Cell" refers to a unit cell in which a=b=c; and $\alpha=\beta=\gamma \neq 90°$.

[0116] "Trigonal/Hexagonal Unit Cell" refers to a unit cell in which $a=b\neq c$; $\alpha=\beta=90°$; and $\gamma=120°$.

[0117] "Cubic Unit Cell" refers to a unit cell in which a=b=c; and $\alpha=\beta=\gamma=90°$.

[0118] "Crystal Lattice" refers to the array of points defined by the vertices of packed unit cells.

[0119] "Space Group" refers to the set of symmetry operations of a unit cell. In a space group designation (*e.g.*, C2) the capital letter indicates the lattice type and the other symbols represent symmetry operations that may be carried out on the unit cell without changing its appearance.

[0120] "Asymmetric Unit" refers to the largest aggregate of molecules in the unit cell that possesses no symmetry elements that are part of the space group symmetry, but that may be juxtaposed on other identical entities by symmetry operations.

[0121] "Crystallographically-Related Dimer (or oligomer)" refers to a dimer (or oligomer, such as, for example, a trimer or a tetramer) of two (or more) molecules wherein the symmetry axes or planes that relate the two (or more) molecules comprising the dimer (or oligomer) coincide with the symmetry axes or planes of the crystal lattice.

[0122] "Non-Crystallographically-Related Dimer (or oligomer)" refers to a dimer (or oligomer, such as, for example, a trimer or a tetramer) of two (or more) molecules wherein the symmetry axes or planes that relate the two (or more) molecules comprising the dimer (or oligomer) do not coincide with the symmetry axes or planes of the crystal lattice.

[0123] "Isomorphous Replacement" refers to the method of using heavy-atom derivative crystals to obtain the phase information necessary to elucidate the three-dimensional structure of a crystallized polypeptide (Blundell *et al.*, Protein Crystallography, Academic Press, esp. pp. 151-64, 1976; Methods in Enzymology 276:361-557, Academic Press, 1997). The phrase "heavy-atom derivatization" is synonymous with "isomorphous replacement."

[0124] "Multi-Wavelength Anomalous Dispersion or MAD" refers to a crystallographic technique in which X-ray diffraction data are collected at several different wavelengths from a single heavy-atom derivative crystal, wherein the heavy atom has absorption edges near the energy of incoming X-ray radiation. The resonance between X-

rays and electron orbitals leads to differences in X-ray scattering from absorption of the X-rays (known as anomalous scattering) and permits the locations of the heavy atoms to be identified, which in turn provides phase information for a crystal of a polypeptide. A detailed discussion of MAD analysis may be found in Hendrickson, Trans. Am. Crystallogr. Assoc., 21:11, 1985; Hendrickson *et al.*, EMBO J. 9:1665, 1990; and Hendrickson, Science, 254:51-58, 1991.

[0125] "Single Wavelength Anomalous Dispersion or SAD" refers to a crystallographic technique in which X-ray diffraction data are collected at a single wavelength from a single native or heavy-atom derivative crystal, and phase information is extracted using anomalous scattering information from atoms such as sulfur or chlorine in the native crystal or from the heavy atoms in the heavy-atom derivative crystal. The wavelength of X-rays used to collect data for this phasing technique needs to be close to the absorption edge of the anomalous scatterer. A detailed discussion of SAD analysis may be found in Brodersen, et al., Acta Cryst., D56:431-41, 2000.

[0126] "Single Isomorphous Replacement With Anomalous Scattering or SIRAS" refers to a crystallographic technique that combines isomorphous replacement and anomalous scattering techniques to provide phase information for a crystal of a polypeptide. X-ray diffraction data are collected at a single wavelength, usually from a single heavy-atom derivative crystal. Phase information obtained only from the location of the heavy atoms in a single heavy-atom derivative crystal leads to an ambiguity in the phase angle, which is resolved using anomalous scattering from the heavy atoms. Phase information is therefore extracted from both the location of the heavy atoms and from anomalous scattering of the heavy atoms. A detailed discussion of SIRAS analysis may be found in North, Acta Cryst. 18:212-16, 1965; Matthews, Acta Cryst., 20:82-86, 1966.

[0127] "Molecular Replacement" refers to the method using the structure coordinates of a known polypeptide to calculate initial phases for a new crystal of a polypeptide whose structure coordinates are unknown. This is done by orienting and positioning a polypeptide whose structure coordinates are known within the unit cell of the new crystal. Phases are then calculated from the oriented and positioned polypeptide and combined with observed amplitudes to provide an approximate Fourier synthesis of the structure of the polypeptides comprising the new crystal. The model is then refined to provide a refined set of structure coordinates for the new crystal (Lattman, Methods in Enzymology, 115:55-77, 1985; Rossmann, "The Molecular Replacement Method," Int. Sci. Rev. Ser.

No. 13, Gordon & Breach, New York, 1972; Methods in Enzymology, Vols. 276, 277 (Academic Press, San Diego 1997)). Molecular replacement may be used, for example, to determine the structure coordinates of a crystalline mutant or homolog of PAK6KD using the structure coordinates of PAK6KD.

[0128] "Structure coordinates" refers to mathematical coordinates derived from mathematical equations related to the patterns obtained on diffraction of a monochromatic beam of X-rays by the atoms (scattering centers) of a PAK6KD in crystal form. The diffraction data are used to calculate an electron density map of the repeating unit of the crystal. The electron density maps are used to establish the positions of the individual atoms within the unit cell of the crystal.

[0129] "Having substantially the same three-dimensional structure" refers to a polypeptide that is characterized by a set of molecular structure coordinates that have a root mean square deviation (r.m.s.d.) of up to about or equal to 1.5Å, preferably 1.25Å, preferably 1Å, and preferably 0.5Å, and preferably 0.25Å, when superimposed onto the molecular structure coordinates of Fig. 4 when at least 50% to 100% of the C-alpha atoms of the coordinates are included in the superposition. The program MOE may be used to compare two structures (Chemical Computing Group, Inc., Montreal, Canada). Where structure coordinates are not available for a particular amino acid residue(s), those coordinates are not included in the calculation.

[0130] "α-C" or "α-carbon" or "CA" as used herein, "α-C" or "α-carbon" refer to the alpha carbon of an amino acid residue.

[0131] "α-helix" refers to the conformation of a polypeptide chain in the form of a spiral chain of amino acids stabilized by hydrogen bonds.

[0132] The term "β-sheet" refers to the conformation of a polypeptide chain stretched into an extended zig-zag conformation. Portions of polypeptide chains that run "parallel" all run in the same direction. Where polypeptide chains are "antiparallel," neighboring chains run in opposite directions from each other. The term "run" refers to the N to COOH direction of the polypeptide chain.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline PAK6

[0133] Both native and heavy-atom derivative crystals, such as those obtained from selenium methionine derivative PAK6KD may be used to obtain the molecular structure coordinates of the present invention.

[0134] The PAK6 comprising the crystals of the invention may be isolated from any bacterial, plant, or animal source in which PAK6 is present. Within the scope of the present invention are proteins that are homologous to PAK6 that are derived from any biological kingdom. The PAK6 may be derived from a mammalian source, such as, for example, Homo sapiens. The crystals may comprise wild-type PAK6 or mutants of wild-type PAK6. Mutants of wild-type PAK6 are obtained by replacing at least one amino acid residue in the sequence of the wild-type PAK6 with a different amino acid residue, or by adding or deleting one or more amino acid residues within the wild-type sequence and/or at the N- and/or C-terminus of the wild-type PAK6. The mutants may, but not necessarily, crystallize under crystallization conditions that are substantially similar to those used to crystallize the wild-type PAK6.

[0135] The types of mutants contemplated by this invention include, but are not limited to, conservative mutants, non-conservative mutants, deletion mutants, truncated mutants, extended mutants, methionine mutants, selenomethionine mutants, cysteine mutants and selenocysteine mutants. A mutant may have, but need not display, PAK6 activity. A mutant may, for example, display biological activity that is substantially similar to that of the wild-type polypeptide. Methionine, selenomethione, cysteine, and selenocysteine mutants are particularly useful for producing heavy-atom derivative crystals, as described in detail, below.

[0136] It will be recognized by one of skill in the art that the types of mutants contemplated herein are not mutually exclusive; that is, for example, a polypeptide having a conservative mutation in one amino acid may in addition have a truncation of residues at the N-terminus, and several Ala, Leu, or Ile→Met mutations.

[0137] Sequence alignments of polypeptides in a protein family or of homologous polypeptide domains may be used to identify potential amino acid residues in the polypeptide sequence that are candidates for mutation. Identifying mutations that do not significantly interfere with the three-dimensional structure of PAK6 and/or that do not

deleteriously affect, and that may even enhance, the activity of PAK6 will depend, in part, on the region where the mutation occurs. In highly variable regions of the molecule, non-conservative substitutions as well as conservative substitutions may be tolerated without significantly disrupting the folding, the three-dimensional structure and/or the biological activity of the molecule. In highly conserved regions, or regions containing significant secondary structure, conservative amino acid substitutions may be tolerated.

[0138] Conservative amino acid substitutions are well known in the art, and include substitutions made on the basis of a similarity in polarity, charge, solubility, hydrophobicity and/or the hydrophilicity of the amino acid residues involved. Typical conservative substitutions are those in which the amino acid is substituted with a different amino acid that is a member of the same class or category, as those classes are defined herein. Thus, typical conservative substitutions include aromatic to aromatic, apolar to apolar, aliphatic to aliphatic, acidic to acidic, basic to basic, polar to polar, etc. Other conservative amino acid substitutions are well known in the art. It will be recognized by those of skill in the art that generally, a total of 20% or fewer, typically 10% or fewer, most usually 5% or fewer, of the amino acids in the wild-type polypeptide sequence may be conservatively substituted with other amino acids without deleteriously affecting the biological activity, the folding, and/or the three-dimensional structure of the molecule, provided that such substitutions do not involve residues that are critical for activity, for example, critical binding pocket residues.

[0139] In some embodiments, it may be desirable to make mutations in the active site of a protein, *e.g.*, to reduce or completely eliminate protein activity. For example, it may be desirable to mutate important residues in the active site of a protease in order to reduce or eliminate protease activity and to avoid autolysis in solution or in a crystal. Thus, for example, in aspartyl proteases, the active site Asp residue may be mutated to an Ala or Asn residue to reduce protease activity. The active site Ser residue in serine proteases may be mutated to an Ala, Cys or Thr residue to reduce or eliminate protease activity. Similarly, the activity of a cysteine protease may be reduced or eliminated by mutating the active site Cys residue to an Ala, Ser or Thr residue. Other mutations that will reduce or completely eliminate the activity of a particular protein will be apparent to those of skill in the art.

[0140] The amino acid residue Cys (C) is unusual in that it can form disulfide bridges with other Cys (C) residues or other sulfhydryls, such as, for example, sulfhydryl-

containing amino acids ("cysteine-like amino acids"). The ability of Cys (C) residues and other cysteine-like amino acids to exist in a polypeptide in either the reduced free -SH or oxidized disulfide-bridged form affects whether Cys (C) residues contribute net hydrophobic or hydrophilic character to a polypeptide. While Cys (C) exhibits a hydrophobicity of 0.29 according to the consensus scale of Eisenberg (Eisenberg *et al.*, J. Mol. Biol. 179:125-42, 1984), it is to be understood that for purposes of the present invention Cys (C) is categorized as a polar hydrophilic amino acid, notwithstanding the general classifications defined above. For example, Cys residues that are known to participate in disulfide bridges are not substituted or are conservatively substituted with other cysteine-like amino acids so that the residue can participate in a disulfide bridge. Typical cysteine-like residues include, for example, Pen, hCys, etc. Substitutions for Cys residues that interfere with crystallization are discussed *infra.*

[0141] The structural coordinates of a binding pocket and/or of the protein may be used, for example, to engineer new molecules. These new molecules may be expressed in cells, for example, in plant cells using, for example, gene transformation, to improve nutrient yields in plant crops or to use plants to produce new molecules.

[0142] While in most instances the amino acids of PAK6KD will be substituted with genetically-encoded amino acids, in certain circumstances mutants may include non-genetically encoded amino acids. For example, non-encoded derivatives of certain encoded amino acids, such as SeMet and/or SeCys, may be incorporated into the polypeptide chain using biological expression systems (such SeMet and SeCys mutants are described in more detail, *infra*).

[0143] Alternatively, in instances where the mutant will be prepared in whole or in part by chemical synthesis, virtually any non-encoded amino acids may be used, ranging from D-isomers of the genetically encoded amino acids to non-encoded naturally-occurring natural and synthetic amino acids.

[0144] Conservative amino acid substitutions for many of the commonly known non-genetically encoded amino acids are well known in the art. Conservative substitutions for other non-encoded amino acids may be determined based on their physical properties as compared to the properties of the genetically encoded amino acids.

[0145] Those of ordinary skill in the art will recognize that substitutions, additions, and/or deletions that do not substantially alter the three dimensional structure of PAK6KD and that, for example, do not substantially alter the three dimensional structure of the

PAK6KD binding pocket or pockets discussed in the present application, are within the scope of the present invention. Such substitutions, additions, and/or deletions may be useful, for example, to provide convenient cloning sites in cDNA encoding PAK6, to aid in its purification, or to aid in obtaining crystallization.

[0146] These substitutions, deletions and/or additions include, but are not limited to, His tags, intein-containing self-cleaving tags, maltose binding protein fusions, glutathione S-transferase protein fusions, antibody fusions, green fluorescent protein fusions, signal peptide fusions, biotin accepting peptide fusions, tags that contain protease cleavage sites, and the like. Mutations may also be introduced into a polypeptide sequence where there are residues, *e.g.*, cysteine residues that interfere with crystallization. These cysteine residues may be substituted with an appropriate amino acid that does not readily form covalent bonds with other amino acid residues under crystallization conditions; *e.g.*, by substituting the cysteine with Ala, Ser or Gly. Any cysteine located in a non-helical or non-stranded segment, based on secondary structure assignments, are good candidates for replacement.

[0147] Mutants within the scope of the invention may or may not have PAK6 activity. Amino acid substitutions, additions and/or deletions that might alter or inhibit PAK6 activity are within the scope of the present invention. These mutants may be used in their crystalline form, or the molecular structure coordinates obtained therefrom, for example, to determine PAK6 structure and/or to provide phase information to aid the determination of the three-dimensional X-ray structures of other related or non-related crystalline polypeptides.

[0148] The heavy-atom derivative crystals from which the molecular structure coordinates of the invention are obtained generally comprise a crystalline PAK6KD polypeptide in association with one or more heavy atoms, such as, for example, Xe, Kr, Br, I, or a heavy metal atom. The polypeptide may correspond to a wild-type or a mutant PAK6KD, which may optionally be in co-complex with one or more molecules, as previously described. There are various types of heavy-atom derivatives of polypeptides: heavy-atom derivatives resulting from exposure of the protein to a heavy atom in solution, wherein crystals are grown in medium comprising the heavy atom, or in crystalline form, wherein the heavy atom diffuses into the crystal, heavy-atom derivatives wherein the polypeptide comprises heavy-atom containing amino acids, *e.g.*, selenomethionine and/or

selenocysteine, and heavy atom derivatives where the heavy atom is forced in under pressure, such as, for example, in a xenon chamber.

[0149] In practice, heavy-atom derivatives of the first type may be formed by soaking a native crystal in a solution comprising heavy metal atom salts, or organometallic compounds, *e.g.*, lead chloride, gold thiomalate, ethylmercurithiosalicylic acid-sodium salt (thimerosal), uranyl acetate, platinum tetrachloride, osmium tetraoxide, zinc sulfate, and cobalt hexamine, which can diffuse through the crystal and bind to the crystalline polypeptide.

[0150] Heavy-atom derivatives of this type can also be formed by adding to a crystallization solution comprising the polypeptide to be crystallized, an amount of a heavy metal atom salt, which may associate with the protein and be incorporated into the crystal. The location(s) of the bound heavy metal atom(s) may be determined by X-ray diffraction analysis of the crystal. This information, in turn, is used to generate the phase information needed to construct the three-dimensional structure of the protein.

[0151] Heavy-atom derivative crystals may also be prepared from polypeptides that include one or more SeMet and/or SeCys residues (SeMet and/or SeCys mutants). Such selenocysteine or selenomethionine mutants may be made from wild-type or mutant PAK6KD by expression of PAK6KD-encoding cDNAs in auxotrophic *E. coli* strains (Hendrickson *et al.*, EMBO J. 9(5):1665-72, 1990). In this method, the wild-type or mutant PAK6KD cDNA may be expressed in a host organism on a growth medium depleted of either natural cysteine or methionine (or both) but enriched in selenocysteine or selenomethionine (or both). Alternatively, selenocysteine or selenomethionine mutants may be made using nonauxotrophic *E. coli* strains, *e.g.*, by inhibiting methionine biosynthesis in these strains with high concentrations of Ile, Lys, Phe, Leu, Val or Thr and then providing selenomethionine in the medium (Doublié, Methods in Enzymology, 276:523-30, 1997). Furthermore, selenocysteine may be selectively incorporated into polypeptides by exploiting the prokaryotic and eukaryotic mechanisms for selenocysteine incorporation into certain classes of proteins *in vivo*, as described in U.S. Patent No. 5,700,660 to Leonard *et al.* (filed June 7, 1995). One of skill in the art will recognize that selenocysteine may, for example, not incorporated in place of cysteine residues that form disulfide bridges, as these may be important for maintaining the three-dimensional structure of the protein and may, for example, not be eliminated. One of skill in the art will further recognize that, in order to obtain accurate phase information, approximately

one selenium atom should be incorporated for every 140 amino acid residues of the polypeptide chain. The number of selenium atoms incorporated into the polypeptide chain may be conveniently controlled by designing a Met or Cys mutant having an appropriate number of Met and/or Cys residues, as described more fully below.

[0152] In some instances, the polypeptide to be crystallized may not contain cysteine or methionine residues. Therefore, if selenomethionine and/or selenocysteine mutants are to be used to obtain heavy-atom derivative crystals, methionine and/or cysteine residues may be introduced into the polypeptide chain. Likewise, Cys residues must be introduced into the polypeptide chain if the use of a cysteine-binding heavy metal, such as mercury, is contemplated for production of a heavy-atom derivative crystal.

[0153] Such mutations are, for example, introduced into the polypeptide sequence at sites that will not disturb the overall protein fold. For example, a residue that is conserved among many members of the protein family or that is thought to be involved in maintaining its activity or structural integrity, as determined by, *e.g.*, sequence alignments, should not be mutated to a Met or Cys. In addition, conservative mutations, such as Ser to Cys, or Leu or Ile to Met, are, for example, introduced. One additional consideration is that, in order for a heavy-atom derivative crystal to provide phase information for structure determination, the location of the heavy atom(s) in the crystal unit cell must be determinable and provide phase information. Therefore, a mutation is, for example, not introduced into a portion of the protein that is likely to be mobile, *e.g.*, at, or within 1-5 residues of, the N- and C-termini, or within loops.

[0154] Conversely, if there are too many methionine and/or cysteine residues in a polypeptide sequence, over-incorporation of the selenium-containing side chains can lead to the inability of the polypeptide to fold and/or crystallize, and may potentially lead to complications in solving the crystal structure. In this case, methionine and/or cysteine mutants are prepared by substituting one or more of these Met and/or Cys residues with another residue. The considerations for these substitutions are the same as those discussed above for mutations that introduce methionine and/or cysteine residues into the polypeptide. Specifically, the Met and/or Cys residues are, for example, conservatively substituted with Leu/Ile and Ser, respectively.

[0155] As DNA encoding cysteine and methionine mutants may be used in the methods described above for obtaining SeCys and SeMet heavy-atom derivative crystals, the Cys or Met mutant may have, for example, one Cys or Met residue for every 140 amino acids.

Production of Polypeptides

[0156] The native and mutated PAK6KD or PAK6 polypeptides described herein may be chemically synthesized in whole or part using techniques that are well known in the art (see, *e.g.*, Creighton, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., NY, 1983).

[0157] Gene expression systems may be used for the synthesis of native and mutated polypeptides. Expression vectors containing the native or mutated polypeptide coding sequence and appropriate transcriptional/translational control signals, that are known to those skilled in the art may be constructed. These methods include *in vitro* recombinant DNA techniques, synthetic techniques and *in vivo* recombination/genetic recombination. See, for example, the techniques described in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY, 2001, and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY, 1989.

[0158] Host-expression vector systems may be used to express PAK6KD or PAK6. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing the coding sequence; yeast transformed with recombinant yeast expression vectors containing the coding sequence; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing the coding sequence; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing the coding sequence; or animal cell systems. The protein may also be expressed in human gene therapy systems, including, for example, expressing the protein to augment the amount of the protein in an individual, or to express an engineered therapeutic protein. The expression elements of these systems vary in their strength and specificities.

[0159] Specifically designed vectors allow the shuttling of DNA between hosts such as bacteria-yeast or bacteria-animal cells. An appropriately constructed expression vector may contain: an origin of replication for autonomous replication in host cells, one or more selectable markers, a limited number of useful restriction enzyme sites, a potential for high copy number, and active promoters. A promoter is defined as a DNA sequence that

directs RNA polymerase to bind to DNA and initiate RNA synthesis. A strong promoter is one that causes mRNAs to be initiated at high frequency.

[0160] The expression vector may also comprise various elements that affect transcription and translation, including, for example, constitutive and inducible promoters. These elements are often host and/or vector dependent. For example, when cloning in bacterial systems, inducible promoters such as the T7 promoter, pL of bacteriophage λ, plac, ptrp, ptac (ptrp-lac hybrid promoter) and the like may be used; when cloning in insect cell systems, promoters such as the baculovirus polyhedrin promoter may be used; when cloning in plant cell systems, promoters derived from the genome of plant cells (*e.g.*, heat shock promoters; the promoter for the small subunit of RUBISCO; the promoter for the chlorophyll a/b binding protein) or from plant viruses (*e.g.*, the 35S RNA promoter of CaMV; the coat protein promoter of TMV) may be used; when cloning in mammalian cell systems, mammalian promoters (*e.g.*, metallothionein promoter) or mammalian viral promoters, (*e.g.*, adenovirus late promoter; vaccinia virus 7.5K promoter; SV40 promoter; bovine papilloma virus promoter; and Epstein-Barr virus promoter) may be used.

[0161] Various methods may be used to introduce the vector into host cells, for example, transformation, transfection, infection, protoplast fusion, and electroporation. The expression vector-containing cells are clonally propagated and individually analyzed to determine whether they produce the appropriate polypeptides. Various selection methods, including, for example, antibiotic resistance, may be used to identify host cells that have been transformed. Identification of polypeptide expressing host cell clones may be done by several means, including but not limited to immunological reactivity with anti-PAK6KD or PAK6 antibodies, and the presence of host cell-associated activity.

[0162] Expression of cDNA may also be performed using *in vitro* produced synthetic mRNA. Synthetic mRNA may be efficiently translated in various cell-free systems, including but not limited to wheat germ extracts and reticulocyte extracts, as well as efficiently translated in cell-based systems, including, but not limited, to microinjection into frog oocytes.

[0163] To determine the cDNA sequence(s) that yields optimal levels of activity and/or protein, modified cDNA molecules are constructed. A non-limiting example of a modified cDNA is where the codon usage in the cDNA has been optimized for the host cell in which the cDNA will be expressed. Host cells are transformed with the cDNA molecules and the levels of PAK6KD or PAK6 RNA and/or protein are measured.

[0164] Levels of PAK6 or PAK6KD protein in host cells are quantitated by a variety of methods such as immunoaffinity and/or ligand affinity techniques, PAK6 or PAK6KD-specific affinity beads or specific antibodies are used to isolate ^{35}S-methionine labeled or unlabeled protein. Labeled or unlabeled protein is analyzed by SDS-PAGE. Unlabeled protein is detected by Western blotting, ELISA or RIA employing specific antibodies.

[0165] Following expression of PAK6 or PAK6KD in a recombinant host cell, polypeptides may be recovered to provide the protein in active form. Several purification procedures are available and suitable for use. Recombinant PAK6 or PAK6KD may be purified from cell lysates or from conditioned culture media, by various combinations of, or individual application of, fractionation, or chromatography steps that are known in the art.

[0166] In addition, recombinant PAK6 or PAK6KD may be separated from other cellular proteins by use of an immuno-affinity column made with monoclonal or polyclonal antibodies specific for full length nascent protein or polypeptide fragments thereof. Other affinity based purification techniques known in the art may also be used.

[0167] Alternatively, the polypeptides may be recovered from a host cell in an unfolded, inactive form, *e.g.*, from inclusion bodies of bacteria. Proteins recovered in this form may be solubilized using a denaturant, *e.g.*, guanidinium hydrochloride, and then refolded into an active form using methods known to those skilled in the art, such as dialysis.

Crystallization Of Polypeptides And Characterization Of Crystal

[0168] Various methods known in the art may be used to produce the native and heavy-atom derivative crystals of the present invention. Methods include, but are not limited to, batch, liquid bridge, dialysis, and vapor diffusion (see, *e.g.*, McPherson, Crystallization of Biological Macromolecules, Cold Spring Harbor Press, New York, 1998; McPherson, Eur. J. Biochem. 189:1-23, 1990; Weber, Adv. Protein Chem. 41:1-36, 1991; Methods in Enzymology 276:13-22, 100-110; 131-143, Academic Press, San Diego, 1997).

[0169] Generally, native crystals are grown by dissolving substantially pure polypeptide in an aqueous buffer containing a precipitant at a concentration just below that necessary to precipitate the protein. Examples of precipitants include, but are not limited to, polyethylene glycol, ammonium sulfate, 2-methyl-2,4-pentanediol, sodium citrate, sodium chloride, glycerol, isopropanol, lithium sulfate, sodium acetate, sodium formate,

potassium sodium tartrate, ethanol, hexanediol, ethylene glycol, dioxane, t-butanol and combinations thereof. Water is removed by controlled evaporation to produce precipitating conditions, which are maintained until crystal growth ceases.

[0170] In one embodiment, native crystals are grown by vapor diffusion in hanging drops or sitting drops (McPherson, Preparation and Analysis of Protein Crystals, John Wiley, New York, 1982; McPherson, Eur. J. Biochem. 189:1-23, 1990). Generally, up to about 25 μL, or up to about 5μl, 3μl, or 2μl, of substantially pure polypeptide solution is mixed with a volume of reservoir solution. The ratio may vary according to biophysical conditions, for example, the ratio of protein volume: reservoir volume in the drop may be 1:1, giving a precipitant concentration about half that required for crystallization. Those of ordinary skill in the art recognize that the drop and reservoir volumes may be varied within certain biophysical conditions and still allow crystallization. In the sitting drop method, the polypeptide/precipitant solution is allowed to equilibrate in a closed container with a larger aqueous reservoir having a precipitant concentration optimal for producing crystals. In the hanging drop method, the polypeptide solution mixed with reservoir solution is suspended as a droplet underneath, for example, a coverslip, which is sealed onto the top of the reservoir. For both methods, the sealed container is allowed to stand, usually, for example, for up to 2-6 weeks, until crystals grow. The drop may be checked periodically to determine if a crystal has formed. One way of viewing the drop is using, for example, a microscope. One method of checking the drop, for high throughput purposes, includes methods that may be found in, for example, U.S. Utility Patent Application 10/042,929, filed October 18, 2001, entitled "Apparatus and Method for Identification of Crystals By In-situ X-Ray Diffraction." Such methods include, for example, using an automated apparatus comprising a crystal growing incubator, an X-ray source adjacent to the crystal growing incubator, where the X-ray source is configured to irradiate the crystalline material grown in the crystal growing incubator, and an X-ray detector configured to detect the presence of the diffracted X-rays from crystalline material grown in the incubator. In some examples, a charge coupled video camera is included in the detector system.

[0171] Those having skill in the art will recognize that the above-described crystallization conditions may be varied. Such variations may be used alone or in combination, and may include various volumes of protein solution and reservoir solution known to those of ordinary skill in the art. Other buffer solutions may be used such as

Tris, imidazole, or MOPS buffer, so long as the desired pH range is maintained, and the chemical composition of the buffer is compatible with crystal formation. Compounds or other ligands may be added to the crystallization solution in order to obtain co-crystals.

[0172] Heavy-atom derivative crystals may be obtained by soaking native crystals in mother liquor containing salts of heavy metal atoms and can also be obtained from SeMet and/or SeCys mutants, as described above for native crystals.

[0173] Mutant proteins may crystallize under slightly different crystallization conditions than wild-type protein, or under very different crystallization conditions, depending on the nature of the mutation, and its location in the protein. For example, a non-conservative mutation may result in alteration of the hydrophilicity of the mutant, which may in turn make the mutant protein either more soluble or less soluble than the wild-type protein. Typically, if a protein becomes more hydrophilic as a result of a mutation, it will be more soluble than the wild-type protein in an aqueous solution and a higher precipitant concentration will be needed to cause it to crystallize. Conversely, if a protein becomes less hydrophilic as a result of a mutation, it will be less soluble in an aqueous solution and a lower precipitant concentration will be needed to cause it to crystallize. If the mutation happens to be in a region of the protein involved in crystal lattice contacts, crystallization conditions may be affected in more unpredictable ways.

Characterization of Crystals

[0174] The dimensions of a unit cell of a crystal are defined by six numbers, the lengths of three unique edges, a, b, and c, and three unique angles α, β, and γ. The type of unit cell that comprises a crystal is dependent on the values of these variables, as discussed above.

[0175] When a crystal is exposed to an X-ray beam, the electrons of the molecules in the crystal diffract the beam such that there is a sphere of diffracted X-rays around the crystal. The angle at which diffracted beams emerge from the crystal may be computed by treating diffraction as if it were reflection from sets of equivalent, parallel planes of atoms in a crystal (Bragg's Law). The most obvious sets of planes in a crystal lattice are those that are parallel to the faces of the unit cell. These and other sets of planes may be drawn through the lattice points. Each set of planes is identified by three indices, hkl. The h index gives the number of parts into which the a edge of the unit cell is cut, the k index gives the number of parts into which the b edge of the unit cell is cut, and the l index gives

the number of parts into which the c edge of the unit cell is cut by the set of hkl planes. Thus, for example, the 235 planes cut the a edge of each unit cell into halves, the b edge of each unit cell into thirds, and the c edge of each unit cell into fifths. Planes that are parallel to the bc face of the unit cell are the 100 planes; planes that are parallel to the ac face of the unit cell are the 010 planes; and planes that are parallel to the ab face of the unit cell are the 001 planes.

[0176] When a detector is placed in the path of the diffracted X-rays, in effect cutting into the sphere of diffraction, a series of spots, or reflections, may be recorded of a still crystal (not rotated) to produce a "still" diffraction pattern. Each reflection is the result of X-rays reflecting off one set of parallel planes, and is characterized by an intensity, which is related to the distribution of molecules in the unit cell, and hkl indices, which correspond to the parallel planes from which the beam producing that spot was reflected. If the crystal is rotated about an axis perpendicular to the X-ray beam, a large number of reflections are recorded on the detector, resulting in a diffraction pattern.

[0177] The unit cell dimensions and space group of a crystal may be determined from its diffraction pattern. First, the spacing of reflections is inversely proportional to the lengths of the edges of the unit cell. Therefore, if a diffraction pattern is recorded when the X-ray beam is perpendicular to a face of the unit cell, two of the unit cell dimensions may be deduced from the spacing of the reflections in the x and y directions of the detector, the crystal-to-detector distance, and the wavelength of the X-rays. Those of skill in the art will appreciate that, in order to obtain all three unit cell dimensions, the crystal must be rotated such that the X-ray beam is perpendicular to another face of the unit cell. Second, the angles of a unit cell may be determined by the angles between lines of spots on the diffraction pattern. Third, the absence of certain reflections and the repetitive nature of the diffraction pattern, which may be evident by visual inspection, indicate the internal symmetry, or space group, of the crystal. Therefore, a crystal may be characterized by its unit cell and space group, as well as by its diffraction pattern.

[0178] Once the dimensions of the unit cell are determined, the likely number of polypeptides in the asymmetric unit may be deduced from the size of the polypeptide, the density of the average protein, and the typical solvent content of a protein crystal, which is usually in the range of 30-70% of the unit cell volume (Matthews, J. Mol. Biol. 33(2):491-97, 1968).

Collection of Data and Determination of Structure Solutions

[0179] The diffraction pattern is related to the three-dimensional shape of the molecule by a Fourier transform. The process of determining the solution is in essence a re-focusing of the diffracted X-rays to produce a three-dimensional image of the molecule in the crystal. Since re-focusing of X-rays cannot be done with a lens at this time, it is done via mathematical operations.

[0180] The sphere of diffraction has symmetry that depends on the internal symmetry of the crystal, which means that certain orientations of the crystal will produce the same set of reflections. Thus, a crystal with high symmetry has a more repetitive diffraction pattern, and there are fewer unique reflections that need to be recorded in order to have a complete representation of the diffraction. The goal of data collection, a dataset, is a set of consistently measured, indexed intensities for as many reflections as possible. A complete dataset is collected if at least 80%, preferably at least 90%, most preferably at least 95% of unique reflections are recorded. In one embodiment, a complete dataset is collected using one crystal. In another embodiment, a complete dataset is collected using more than one crystal of the same type.

[0181] Sources of X-rays include, but are not limited to, a rotating anode X-ray generator such as a Rigaku RU-200, a micro source or mini-source, a sealed-beam source, or a beam line at a synchrotron light source, such as the Advanced Photon Source at Argonne National Laboratory. Suitable detectors for recording diffraction patterns include, but are not limited to, X-ray sensitive film, multiwire area detectors, image plates coated with phosphorus, and CCD cameras. Typically, the detector and the X-ray beam remain stationary, so that, in order to record diffraction from different parts of the crystal's sphere of diffraction, the crystal itself is moved via an automated system of moveable circles called a goniostat.

[0182] One of the biggest problems in data collection, particularly from macromolecular crystals having a high solvent content, is the rapid degradation of the crystal in the X-ray beam. In order to slow the degradation, data is often collected from a crystal at liquid nitrogen temperatures. In order for a crystal to survive the initial exposure to liquid nitrogen, the formation of ice within the crystal may be prevented by the use of a cryoprotectant. Suitable cryoprotectants include, but are not limited to, low molecular weight polyethylene glycols, ethylene glycol, sucrose, glycerol, xylitol, and combinations thereof. Crystals may be soaked in a solution comprising the one or more cryoprotectants

prior to exposure to liquid nitrogen, or the one or more cryoprotectants may be added to the crystallization solution. Data collection at liquid nitrogen temperatures may allow the collection of an entire dataset from one crystal.

[0183] Once a dataset is collected, the information is used to determine the three-dimensional structure of the molecule in the crystal. This phase information may be acquired by methods described below in order to perform a Fourier transform on the diffraction pattern to obtain the three-dimensional structure of the molecule in the crystal. It is the determination of phase information that in effect refocuses X-rays to produce the image of the molecule.

[0184] One method of obtaining phase information is by isomorphous replacement, in which heavy-atom derivative crystals are used. In this method, the positions of heavy atoms bound to the molecules in the heavy-atom derivative crystal are determined, and this information is then used to obtain the phase information necessary to elucidate the three-dimensional structure of a native crystal (Blundell *et al.*, Protein Crystallography, Academic Press, 1976).

[0185] Another method of obtaining phase information is by molecular replacement, which is a method of calculating initial phases for a new crystal of a polypeptide whose structure coordinates are unknown by orienting and positioning a polypeptide whose structure coordinates are known within the unit cell of the new crystal so as to best account for the observed diffraction pattern of the new crystal. Phases are then calculated from the oriented and positioned polypeptide and combined with observed amplitudes to provide an approximate Fourier synthesis of the structure of the molecules comprising the new crystal (Lattman, Methods in Enzymology 115:55-77, 1985; Rossmann, "The Molecular Replacement Method," Int. Sci. Rev. Ser. No. 13, Gordon & Breach, New York, 1972).

[0186] A third method of phase determination is multi-wavelength anomalous diffraction or MAD. In this method, X-ray diffraction data are collected at several different wavelengths from a single crystal containing at least one heavy atom with absorption edges near the energy of incoming X-ray radiation. The resonance between X-rays and electron orbitals leads to differences in X-ray scattering that permits the locations of the heavy atoms to be identified, which in turn provides phase information for a crystal of a polypeptide. A detailed discussion of MAD analysis may be found in Hendrickson,

Trans. Am. Crystallogr. Assoc., 21:11, 1985; Hendrickson *et al.*, EMBO J. 9:1665, 1990; and Hendrickson, Science, 254:51-58, 1991).

[0187] A fourth method of determining phase information is single wavelength anomalous dispersion or SAD. In this technique, X-ray diffraction data are collected at a single wavelength from a single native or heavy-atom derivative crystal, and phase information is extracted using anomalous scattering information from atoms such as sulfur or chlorine in the native crystal or from the heavy atoms in the heavy-atom derivative crystal. The wavelength of X-rays used to collect data for this phasing technique need not be close to the absorption edge of the anomalous scatterer. A detailed discussion of SAD analysis may be found in Brodersen, et al., Acta Cryst., D56:431-41, 2000.

[0188] A fifth method of determining phase information is single isomorphous replacement with anomalous scattering or SIRAS. SIRAS combines isomorphous replacement and anomalous scattering techniques to provide phase information for a crystal of a polypeptide. X-ray diffraction data are collected at a single wavelength, usually from both a native and a single heavy-atom derivative crystal. Phase information obtained only from the location of the heavy atoms in a single heavy-atom derivative crystal leads to an ambiguity in the phase angle, which is resolved using anomalous scattering from the heavy atoms. Phase information is extracted from both the location of the heavy atoms and from anomalous scattering of the heavy atoms. A detailed discussion of SIRAS analysis may be found in North, Acta Cryst. 18:212-16, 1965; Matthews, Acta Cryst. 20:82-86, 1966; Methods in Enzymology 276:530-37, 1997.

[0189] Once phase information is obtained, it is combined with the diffraction data to produce an electron density map, an image of the electron clouds surrounding the atoms that constitute the molecules in the unit cell. The higher the resolution of the data, the more distinguishable the features of the electron density map, because atoms that are closer together are resolvable. A model of the macromolecule is then built into the electron density map with the aid of a computer, using as a guide all available information, such as the polypeptide sequence and the established rules of molecular structure and stereochemistry. Interpreting the electron density map is a process of finding the chemically reasonable conformation that fits the map precisely.

[0190] After a model is generated, a structure is refined. Refinement is the process of minimizing the function ϕ, which is the difference between observed and calculated intensity values (measured by an R-factor), and which is a function of the position,

temperature factor, and occupancy of each non-hydrogen atom in the model. This usually involves alternate cycles of real space refinement, *i.e.*, calculation of electron density maps and model building, and reciprocal space refinement, *i.e.*, computational attempts to improve the agreement between the original intensity data and intensity data generated from each successive model. Refinement ends when the function ϕ converges on a minimum wherein the model fits the electron density map and is stereochemically and conformationally reasonable. During the last stages of refinement, ordered solvent molecules are added to the structure.

Structures of PAK6KD

[0191] The present invention provides, for the first time, the high-resolution three-dimensional structures and molecular structure coordinates of crystalline PAK6KD as determined by X-ray crystallography.

[0192] Contemplated within the scope of the present invention are any set of structure coordinates obtained for crystals of PAK6KD, whether native crystals, heavy-atom derivative crystals or co-crystals, that have a root mean square deviation ("r.m.s.d.") of up to about or equal to 1.5Å, preferably 1.25Å, preferably 1Å, preferably 1.75Å, and preferably 0.5Å when superimposed, using backbone atoms (N, C-α, C and O), or using C-α atoms, on the structure coordinates listed in Fig. 4 are considered to be within the scope of the present invention when at least 50% to 100% of the backbone atoms of PAK6KD are included in the superposition. The amino acid numbers in Figure 4 reflect the amino acid position in the expressed protein used to obtain the crystals of the present invention. Those of ordinary skill in the art may align the sequence with other sequences of PAK6KD or PAK6 to, if desired, correlate the amino acid residue number with the Figure 4 sequence or the wild type sequence numbers.

Structure Coordinates

[0193] The molecular structure coordinates may be used in molecular modeling and design, as described more fully below. The present invention encompasses the structure coordinates and other information, *e.g.*, amino acid sequence, connectivity tables, vector-based representations, temperature factors, etc., used to generate the three-dimensional

structure of the polypeptide for use in the software programs described below and other software programs.

[0194] The invention includes methods of producing computer readable databases comprising the three-dimensional molecular structure coordinates of certain molecules, including, for example, the PAK6KD structure coordinates, the structure coordinates of binding pockets or active sites of PAK6KD, or structure coordinates of compounds capable of binding to PAK6KD. The databases of the present invention may comprise any number of sets of molecular structure coordinates for any number of molecules, including, for examples, structure coordinates of one molecule. In other embodiments, the databases of the present invention may comprise structure coordinates of a compound or compounds that have been identified by virtual screening to bind to a PAK6 binding pocket, or other representations of such compounds such as, for example, a graphic representation or a name. By "database" is meant a collection of retrievable data. The invention encompasses machine readable media embedded with or containing information regarding the three-dimensional structure of a crystalline polypeptide and/or model, such as, for example, its molecular structure coordinates, described herein, or with subunits, domains, and/or, portions thereof such as, for example, portions comprising active sites, accessory binding sites, and/or binding pockets in either liganded or unliganded forms. Alternatively, the information may be that of identifiers which represent specific structures found in a protein. As used herein, "machine readable medium" refers to any medium that may be read and accessed directly by a computer or scanner. Such media may take many forms, including but not limited to, non-volatile, volatile and transmission media. Non-volatile media, i.e., media that can retain information in the absence of power, includes a ROM. Volatile media, i.e., media that cannot retain information in the absence of power, includes a main memory. Transmission media includes coaxial cables, copper wire and fiber optics, including the wires that comprise the bus. Transmission media can also take the form of carrier waves; i.e., electromagnetic waves that may be modulated, as in frequency, amplitude or phase, to transmit information signals. Additionally, transmission media can take the form of acoustic or light waves, such as those generated during radio wave and infrared data communications.

[0195] Such media also include, but are not limited to: magnetic storage media, such as floppy discs, flexible discs, hard disc storage medium and magnetic tape; optical storage media such as optical discs or CD-ROM; electrical storage media such as RAM or

ROM, PROM (i.e., programmable read only memory), EPROM (i.e., erasable programmable read only memory), including FLASH-EPROM, any other memory chip or cartridge, carrier waves, or any other medium from which a processor can retrieve information, and hybrids of these categories such as magnetic/optical storage media. Such media further include paper on which is recorded a representation of the molecular structure coordinates, *e.g.*, Cartesian coordinates, that may be read by a scanning device and converted into a format readily accessed by a computer or by any of the software programs described herein by, for example, optical character recognition (OCR) software. Such media also include physical media with patterns of holes, such as, for example, punch cards, and paper tape.

[0196] A variety of data storage structures are available for creating a computer readable medium having recorded thereon the molecular structure coordinates of the invention or portions thereof and/or X-ray diffraction data. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats may be used to store the sequence and X-ray data information on a computer readable medium. Such formats include, but are not limited to, macromolecular Crystallographic Information File ("mmCIF") and Protein Data Bank ("PDB") format (Research Collaboratory for Structural Bioinformatics; www.rcsb.org; Cambridge Crystallographic Data Centre format (www.ccdc.can.ac.uk/support/csd_doc/volume3/z323.html); Structure-data ("SD") file format (MDL Information Systems, Inc.; Dalby, *et al.*, J. Chem. Inf. Comp. Sci., 32:244-55, 1992; and line-notation, *e.g.*, as used in SMILES (Weininger, J. Chem. Inf. Comp. Sci. 28:31-36, 1988). Methods of converting between various formats read by different computer software will be readily apparent to those of skill in the art, *e.g.*, BABEL (v. 1.06, Walters & Stahl, ©1992, 1993, 1994; www.brunel.ac.uk/departments/chem/babel.htm). All format representations of the polypeptide coordinates described herein, or portions thereof, are contemplated by the present invention. By providing computer readable medium having stored thereon the atomic coordinates of the invention, one of skill in the art can routinely access the atomic coordinates of the invention, or portions thereof, and related information for use in modeling and design programs, described in detail below.

[0197] A computer may be used to display the structure coordinates or the three-dimensional representation of the protein or peptide structures, or portions thereof, such

as, for example, portions comprising active sites, accessory binding sites, and/or binding pockets, in either liganded or unliganded form, of the present invention. The term "computer" includes, but is not limited to, mainframe computers, personal computers, portable laptop computers, and personal data assistants ("PDAs") which can store data and independently run one or more applications, i.e., programs. The computer may include, for example, a machine readable storage medium of the present invention, a working memory for storing instructions for processing the machine-readable data encoded in the machine readable storage medium, a central processing unit operably coupled to the working memory and to the machine readable storage medium for processing the machine readable information, and a display operably coupled to the central processing unit for displaying the structure coordinates or the three-dimensional representation. The information contained in the machine-readable medium may be in the form of, for example, X-ray diffraction data, structure coordinates, electron density maps, or ribbon structures. The information may also include such data for co-complexes between a compound and a protein or peptide of the present invention.

[0198] The computers of the present invention may also include, for example, a central processing unit, a working memory which may be, for example, random-access memory (RAM) or "core memory," mass storage memory (for example, one or more disk drives or CD-ROM drives), one or more cathode-ray tube ("CRT") display terminals or one or more LCD displays, one or more keyboards, one or more input lines, and one or more output lines, all of which are interconnected by a conventional bi-directional system bus. Machine-readable data of the present invention may be inputted and/or outputted through a modem or modems connected by a telephone line or a dedicated data line (either of which may include, for example, wireless modes of communication). The input hardware may also (or instead) comprise CD-ROM drives or disk drives. Other examples of input devices are a keyboard, a mouse, a trackball, a finger pad, or cursor direction keys. Output hardware may also be implemented by conventional devices. For example, output hardware may include a CRT, or any other display terminal, a printer, or a disk drive. The CPU coordinates the use of the various input and output devices, coordinates data accesses from mass storage and accesses to and from working memory, and determines the order of data processing steps. The computer may use various software programs to process the data of the present invention. Examples of many of these types of software are discussed throughout the present application.

[0199] Those of skill in the art will recognize that a set of structure coordinates is a relative set of points that define a shape in three dimensions. Therefore, two different sets of coordinates could define the identical or a similar shape. Also, minor changes in the individual coordinates may have very little effect on the peptide's shape. Minor changes in the overall structure may have very little to no effect, for example, on the binding pocket, and would not be expected to significantly alter the nature of compounds that might associate with the binding pocket.

[0200] Although Cartesian coordinates are important and convenient representations of the three-dimensional structure of a polypeptide, other representations of the structure are also useful. Therefore, the three-dimensional structure of a polypeptide, as discussed herein, includes not only the Cartesian coordinate representation, but also all alternative representations of the three-dimensional distribution of atoms. For example, atomic coordinates may be represented as a Z-matrix, wherein a first atom of the protein is chosen, a second atom is placed at a defined distance from the first atom, and a third atom is placed at a defined distance from the second atom so that it makes a defined angle with the first atom. Each subsequent atom is placed at a defined distance from a previously placed atom with a specified angle with respect to the third atom, and at a specified torsion angle with respect to a fourth atom. Atomic coordinates may also be represented as a Patterson function, wherein all interatomic vectors are drawn and are then placed with their tails at the origin. This representation is particularly useful for locating heavy atoms in a unit cell. In addition, atomic coordinates may be represented as a series of vectors having magnitude and direction and drawn from a chosen origin to each atom in the polypeptide structure. Furthermore, the positions of atoms in a three-dimensional structure may be represented as fractions of the unit cell (fractional coordinates), or in spherical polar coordinates.

[0201] Additional information, such as thermal parameters, which measure the motion of each atom in the structure, chain identifiers, which identify the particular chain of a multi-chain protein in which an atom is located, and connectivity information, which indicates to which atoms a particular atom is bonded, is also useful for representing a three-dimensional molecular structure.

[0202] The structural information of a compound that binds a PAK6KD of the invention may be similarly stored and transmitted as described above for structural information of PAK6KD.

Uses of the Molecular Structure Coordinates

[0203] Structure information, typically in the form of molecular structure coordinates, may be used in a variety of computational or computer-based methods to, for example, design, screen for, and/or identify compounds that bind the crystallized polypeptide or a portion or fragment thereof, or to intelligently design mutants that have altered biological properties.

[0204] When designing or identifying compounds that may associate with a given protein, binding pockets are often analyzed. The term "binding pocket," refers to a region of a protein that, because of its shape, likely associates with a chemical entity or compound. A binding pocket may be the same as an active site. A binding pocket of a protein is usually involved in associating with the protein's natural ligands or substrates, and is often the basis for the protein's activity. A binding pocket may refer to an active site. Many drugs act by associating with a binding pocket of a protein. A binding pocket may comprise amino acid residues that line the cleft of the pocket. Those of ordinary skill in the art will recognize that the numbering system used for other isoforms of PAK6KD may be different, but that the corresponding amino acids may be determined with a homology software program known to those of ordinary skill in the art. A binding pocket homolog comprises amino acids having structure coordinates that have a root mean square deviation from structure coordinates, as indicated in Fig. 4, of the binding pocket amino acids of up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1Å, preferably up to about 0.75Å, preferably up to about 0.5Å, and preferably up to about 0.25Å.

[0205] Where a binding pocket or regulatory site is said to comprise amino acids having particular structure coordinates, the amino acids comprise the same amino acid residues, or may comprise amino acids having similar properties, as shown in, for example, Table 1, and have either the same relative three-dimensional structure coordinates as Fig. 4, or the group of amino acid residues named as part of the binding pocket have an rmsd of within 1.5Å, preferably within 1.25Å, preferably within 1Å, preferably within 0.75Å, preferably within 0.5Å, and preferably within 0.25Å of the structure coordinates of Fig. 4. Preferably, when comparing the structure coordinates of the backbone atoms of the amino acid residues, the rmsd is within 1.5Å, preferably within

1.25Å, preferably within 1Å, preferably within 0.75Å, preferably within 0.5Å, and more preferably within 0.25Å.

[0206] Software applications are available to compare structures, or portions thereof, to determine if they are sufficiently similar to the structures of the invention such as DALI (Holm and Sander, *J. Mol. Biol.* 233:123-38, 1993; (See European Bioinformatics Institute site at www.ebi.ac.uk/); MOE (Chemical Computing Group, Inc. Montreal, Quebec, Canada; and DEJAVU (Uppsala Software Factory; Kleywegt, G.S. & Jones, T.A., "Detecting Folding Motifs and Similarities in Protein Structure," *Methods in Enzymology*, 277:525-45, 1997).

[0207] The crystals and structure coordinates obtained therefrom may be used for rational drug design to identify and/or design compounds that bind PAK6 as an approach towards developing new therapeutic agents. For example, a high resolution X-ray structure of, for example, a crystallized protein saturated with solvent, will often show the locations of ordered solvent molecules around the protein, and in particular at or near putative binding pockets of the protein. This information can then be used to design molecules that bind these sites, the compounds synthesized and tested for binding in biological assays (Travis, *Science,* 262:1374, 1993).

[0208] The structure may also be computationally screened with a plurality of molecules to determine their ability to bind to the PAK6KD at various sites. Such compounds may be used as targets or leads in medicinal chemistry efforts to identify, for example, inhibitors of potential therapeutic importance (Travis, *Science,* 262:1374, 1993). The three dimensional structures of such compounds may be superimposed on a three dimensional representation of PAK6KD or an active site or binding pocket thereof to assess whether the compound fits spatially into the representation and hence the protein. Structural information produced by such methods and concerning a compound that fits (or a fitting portion of such a compound) may be stored in a machine readable medium. Alternatively, one or more identifiers of a compound that fits, or a fitting portion thereof, may be stored in a machine readable medium. Examples of identifiers include chemical name or abbreviation, chemical or molecular formula, chemical structure, and/or other identifying information. As an non-limiting example, if the three dimensional structure of phenol is found to fit the active site of PAK6KD, the structural information of phenol, or the portion that fits, may be stored for further use. Alternatively, an identifier of phenol, or of the portion that fits, such as the -OH group, may be stored for further use. Other

identifying information for phenol may also be used to represent it. All storage of information concerning a compound that fits may optionally be in combination with one or more pieces of information concerning PAK6KD.

[0209] In an analogous manner, the structure of PAK6KD or an active site or binding pocket thereof may be used to computationally screen small molecule databases for chemical entities or compounds that can bind in whole, or in part, to PAK6. In this screening, the quality of fit of such entities or compounds to the binding pocket may be judged either by shape complementarity or by estimated interaction energy (Meng, *et al.*, *J. Comp. Chem.* 13:505-24, 1992).

[0210] In still another embodiment, compounds may be developed that are analogues of natural substrates, reaction intermediates or reaction products of PAK6. The reaction intermediates of PAK6 may be deduced from the substrates, or reaction products in co-complex with PAK6KD. The binding of substrates, reaction intermediates, and reaction products may change the conformation of the binding pocket, which provides additional information regarding binding patterns of potential ligands, activators, inhibitors, and the like. Such information is also useful to design improved analogues of known PAK6 inhibitors or to design novel classes of inhibitors based on the substrates, reaction intermediates, and reaction products of PAK6KD and PAK6KD-inhibitor co-complexes. This provides a novel route for designing PAK6KD inhibitors with both high specificity and stability.

[0211] Another method of screening or designing compounds that associate with a binding pocket includes, for example, computationally designing a negative image of the binding pocket. This negative image may be used to identify a set of pharmacophores. A pharmacophore may be a description of functional groups and how they relate to each other in three-dimensional space. This set of pharmacophores may be used to design compounds and screen chemical databases for compounds that match with the pharmacophore(s). Compounds identified by this method may then be further evaluated computationally or experimentally for binding activity. Various computer programs may be used to create the negative image of the binding pocket, for example; GRID (Goodford, J. Med. Chem. 28:849-57, 1985; GRID is available from Oxford University, Oxford, UK); MCSS (Miranker & Karplus, Proteins: Structure, Function and Genetics 11:29-34, 1991; MCSS is available from Accelrys, Inc., San Diego, CA); LUDI (Bohm, J. Comp. Aid. Molec. Design 6:61-78, 1992; LUDI is available from Accelrys, Inc., San Diego, CA);

DOCK (Kuntz et al.; *J. Mol. Biol.* 161:269-88, 1982; DOCK is available from University of California, San Francisco, CA); DOCKIT (Metaphorics, Mission Viejo, CA) and MOE. Other appropriate programs are desribed in, for example, Halperin, et al., Proteins 47(4): 409-43 (2002).

[0212] Thus, among the various embodiments of the present invention are methods of identifying, screening, and designing compounds that associate with a binding pocket of PAK6KD.

[0213] The design of compounds that bind to and/or modulate PAK6, for example that inhibit or activate PAK6 according to this invention generally involves consideration of two factors. First, the compound must be capable of physically and structurally associating, either covalently or non-covalently with PAK6. For example, covalent interactions may be important for designing irreversible or suicide inhibitors of a protein. Non-covalent molecular interactions important in the association of PAK6 with the compound include hydrogen bonding, ionic interactions and van der Waals and hydrophobic interactions. Second, the compound must be able to assume a conformation and orientation in relation to the binding pocket, that allows it to associate with PAK6. Although certain portions of the compound will not directly participate in this association with PAK6, those portions may still influence the overall conformation of the molecule and may have a significant impact on potency. Conformational requirements include the overall three-dimensional structure and orientation of the chemical group or compound in relation to all or a portion of the binding pocket, or the spacing between functional groups of a compound comprising several chemical groups that directly interact with PAK6.

[0214] Computer modeling techniques may be used to assess the potential modulating or binding effect of a chemical compound on PAK6KD. If computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to PAK6 and affect (by inhibiting or activating) its activity.

[0215] Modulating or other binding compounds of PAK6 may be computationally evaluated and designed by means of a series of steps in which chemical groups or fragments are screened and selected for their ability to associate with the individual binding pockets or other areas of PAK6. Several methods are available to screen chemical groups or fragments for their ability to associate with PAK6. This process may begin by visual inspection of, for example, the active site on the computer screen based on the **PAK6KD** coordinates. Selected fragments or chemical groups may then be positioned in

a variety of orientations, or docked, within an individual binding pocket of PAK6KD (Blaney, J.M. and Dixon, J.S., *Perspectives in Drug Discovery and Design*, 1:301, 1993). Manual docking may be accomplished using software such as Insight II (Accelrys, San Diego, CA) MOE; CE (Shindyalov, IN, Bourne, PE, "Protein Structure Alignment by Incremental Combinatorial Extension (CE) of the Optimal Path," *Protein Engineering*, 11:739-47, 1998); and SYBYL (Molecular Modeling Software, Tripos Associates, Inc., St. Louis, MO, 1992), followed by energy minimization and molecular dynamics with standard molecular mechanics force fields, such as CHARMM (Brooks, *et al., J. Comp. Chem.* 4:187-217, 1983). More automated docking may be accomplished by using programs such as DOCK (Kuntz *et al., J. Mol. Biol.*, 161:269-88, 1982; DOCK is available from University of California, San Francisco, CA); AUTODOCK (Goodsell & Olsen, Proteins: Structure, Function, and Genetics 8:195-202, 1990; AUTODOCK is available from Scripps Research Institute, La Jolla, CA); GOLD (Cambridge Crystallographic Data Centre (CCDC); Jones et al., *J. Mol. Biol.* 245:43-53, 1995); and FLEXX (Tripos, St. Louis, MO; Rarey, M., et al., *J. Mol. Biol.* 261:470-89, 1996); AMBER (Weiner, *et al., J. Am. Chem. Soc.* 106:765-84, 1984) and C^2 MMFF (Merck Molecular Force Field; Accelrys, San Diego, CA). Other appropriate programs are described in, for example, Halperin, et al.

[0216] Specialized computer programs may also assist in the process of selecting fragments or chemical groups. These include DOCK; GOLD; LUDI; FLEXX (Tripos, St. Louis, MO; Rarey, M., et al., *J. Mol. Biol.* 261:470-89, 1996); and GLIDE (Eldridge, et al., *J. Comput. Aided Mol. Des.* 11:425-45, 1997; Schrödinger, Inc., New York). Other appropriate programs are described in, for example, Halperin, et al., (Portland, OR).

[0217] Once suitable chemical groups or fragments have been selected, they may be assembled into a single compound or inhibitor. Assembly may proceed by visual inspection of the relationship of the fragments to each other in the three-dimensional image displayed on a computer screen in relation to the structure coordinates of **PAK6KD**. This would be followed by manual model building using software such as SYBYL, (Tripos, St. Louis, MO); Insight II (Accelrys, San Diego, CA); and MOE (Chemical Computing Group, Inc., Montreal, Canada). Other appropriate program are described in, for example, Halperin, et al.

[0218] Useful programs to aid one of skill in the art in connecting the individual chemical groups or fragments include, for example:

1. CAVEAT (Bartlett *et al.*, 'CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules'. In Molecular Recognition in Chemical and Biological Problems', Special Pub., *Royal Chem. Soc.* 78:182-96, 1989). CAVEAT is available from the University of California, Berkeley, CA.

2. 3D Database systems such as ISIS or MACCS-3D (MDL Information Systems, San Leandro, Calif.). This area is reviewed in Martin, *J. Med. Chem.* 35:2145-54, 1992).

3. HOOK (Eisen *et al.*, Proteins: Struct., Funct., Genet., 19:199-221, 1994) (available from Accelrys, Inc., San Diego, CA).

4. LUDI (Bohm, J. Comp. Aid. Molec. Design 6:61-78, 1992). LUDI is available from Accelrys, Inc., San Diego, CA.

[0219] Instead of proceeding to build a PAK6 inhibitor in a step-wise fashion one fragment or chemical group at a time, as described above, PAK6 binding compounds may be designed as a whole or 'de novo' using either an empty active site or optionally including some portion(s) of a known inhibitor(s). These methods include, for example:

1. LUDI (Bohm, J. Comp. Aid. Molec. Design 6:61-78, 1992). LUDI is available from Accelrys, Inc., San Diego, CA.

2. LEGEND (Nishibata & Itai, Tetrahedron, 47:8985, 1991). LEGEND is available from Accelrys, Inc., San Diego, CA.

3. LeapFrog (available from Tripos, Inc., St. Louis, Mo.).

4. SPROUT (Gillet *et al.*, J. Comput. Aided Mol. Design 7:127-53, 1993) (available from the University of Leeds, U.K.).

5. GenStar (Murcko, M.A. and Rotstein, S.H. J. Comput. Aided Mol. Des. 7:23-43, 1993).

6. GroupBuild (Rotstein, S.H., and Murcko, M.A., J. Med. Chem. 36:1700, 1993).

7. GrowMol (Rich, D.H. et al., Chimia, 51:45, 1997).

8. Grow (UpJohn; Moon J, Howe W, Proteins, 11:314-28, 1991).

9. SmoG (DeWitte, R.S., Abstr. Pap Am Chem. S. 214:6-Comp Part 1, Sept. 7, 1997; DeWitte, R.S. & Shakhnovich, E.I., J. Am. Chem. Soc. 118:11733-44, 1996).

10. LigBuilder (PDB (www.rcsb.org/pdb); Wang R, Ying G, Lai L, J. Mol. Model. 6: 498-516, 1998).

[0220] Other molecular modeling techniques may also be employed in accordance with this invention. *See, e.g.*, Cohen *et al.*, *J. Med. Chem.* 33:883-94, 1990. *See also*, Navia & Murcko, *Current Opinions in Structural Biology* 2:202-10, 1992; Balbes *et al.*, *Reviews in Computational Chemistry*, 5:337-80, 1994, (Lipkowitz and Boyd, Eds.) (VCH, New York); Guida, *Curr. Opin. Struct. Biol.* 4:777-81, 1994.

[0221] During design and selection of compounds by the above methods, the efficiency with which that compound may bind to PAK6KD may be tested and optimized by computational evaluation. For example, a compound that has been designed or selected to function as a PAK6 inhibitor may occupy a volume not overlapping the volume occupied by the active site residues when the native substrate is bound, however, those of ordinary skill in the art will recognize that there is some flexibility, allowing for rearrangement of the main chains and the side chains. In addition, one of ordinary skill may design compounds that could exploit protein rearrangement upon binding, such as, for example, resulting in an induced fit. An effective PAK6 inhibitor may demonstrate a relatively small difference in energy between its bound and free states (*i.e.*, it must have a small deformation energy of binding and/or low conformational strain upon binding). Thus, the most efficient PAK6 inhibitors should, for example, be designed with a deformation energy of binding of not greater than 10 kcal/mol, for example, not greater than 7 kcal/mol, for example, not greater than 5 kcal/mol and, for example, not greater than 2 kcal/mol. PAK6 inhibitors may interact with the protein in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free compound and the average energy of the conformations observed when the inhibitor binds to the enzyme.

[0222] A compound selected or designed for binding to PAK6KD may be further computationally optimized so that in its bound state it would, for example, lack repulsive electrostatic interaction with the target protein. Non-complementary electrostatic interactions include repulsive charge-charge, dipole-dipole and charge-dipole interactions. Specifically, the sum of all electrostatic interactions between the inhibitor and the protein when the inhibitor is bound to it may make a neutral or favorable contribution to the enthalpy of binding.

[0223] Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 94, revision C (Frisch, Gaussian, Inc., Pittsburgh, PA. ©1995);

AMBER, version 7 (Kollman, University of California at San Francisco, ©2002); QUANTA/CHARMM (Accelrys, Inc., San Diego, CA, ©1995); Insight II/Discover (Accelrys, Inc., San Diego, CA, ©1995); DelPhi (Accelrys, Inc., San Diego, CA, ©1995); and AMSOL (University of Minnesota) (Quantum Chemistry Program Exchange, Indiana University). These programs may be implemented, for instance, using a computer workstation, as are well known in the art, for example, a LINUX, SGI or Sun workstation. Other hardware systems and software packages will be known to those skilled in the art.

[0224] Once a PAK6KD binding compound has been optimally selected or designed, as described above, substitutions may then be made in some of its atoms or chemical groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, *i.e.*, the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. One of skill in the art will understand that substitutions known in the art to alter conformation should be avoided. Such altered chemical compounds may then be analyzed for efficiency of binding to PAK6KD by the same computer methods described in detail above. Methods of structure-based drug design are described in, for example, Klebe, G., J. *Mol. Med.* 78:269-81, 2000); Hol. W.G.J., Angewandte Chemie (Int'l Edition in English) 25:767-852, 1986; and Gane, P.J. and Dean, P.M., *Current Opinion in Structural Biology*, 10:401-04, 2000.

[0225] The present invention also provides means for the preparation of a compound the structure of which has been identified or designed, as described above, as binding PAK6KD or an active site or binding pocket thereof. Where the compound is already known or designed, the synthesis thereof may readily proceed by means known in the art. Alternatively, compounds that match the structure of one or more pharmacophores as described above may be prepared by means known in the art. In an alternative embodiment, the production of a compound may proceed by introduction of one or more desired chemical groups by attachment to an initial compound which binds PAK6KD or an active site or binding pocket thereof and which has, or has been modified to contain, one or more chemical moieties for attachment of one or more desired chemical groups. The initial compound may be viewed as a "scaffold" comprising at least one moiety capable of binding or associating with one or more residues of PAK6KD or an active site or binding pocket thereof.

[0226] The initial compound may be a flexible or rigid "scaffold", optionally containing a linker for introduction of additional chemical moieties. Various scaffold compounds may be used, including, but not limited to, aliphatic carbon chains, pyrrolidinones, sulfonamidopyrrolidinones, cycloalkanonedienes including cyclopentanonedienes, cyclohexanonedienes, and cyclopheptanonedienes, carbazoles, imidazoles, benzimidiazoles, pyridine, isoxazoles, isoxazolines, benzoxazinones, benzamidines, pyridinones and derivatives thereof. Other scaffolds are described in, for example, Klebe, G., *J. Mol. Med.* 78: 269-281 (2000); Maignan, S. and Mikol, V., *Curr. Top. Med. Chem.* 1: 161-174 (2001); and U.S. Patent No. 5,756,466 to Bemis *et al.* The scaffold compound used may, for example, be one that comprises at least one moiety capable of binding or associating with one or more residues of PAK6KD or an active site or binding pocket thereof.

[0227] Chemical moieties on the scaffold compound that permit attachment of one or more desired functional chemical groups may undergo conventional reactions by coupling, substitution, and electrophilic or nucleophilic displacement. For example, the moieties may be those already present on the compound or readily introduced. Alternatively, an variant of the scaffold compound comprising the moieties is utilized initially. As a non-limiting example, the moiety may be a leaving group which can readily be removed from the scaffold compound. Various moieties may be used, including but not limited to pyrophosphates, acetates, hydroxy groups, alkoxy groups, tosylates, brosylates, halogens, and the like. In another embodiment of the invention, the scaffold compound is synthesized from readily available starting materials using conventional techniques. (*See e.g.*, U.S. Patent 5,756,466 for general synthetic methods). Chemical groups are then introduced into the scaffold compound to increase the number of interactions with one or more residues of PAK6KD or an active site or binding pocket thereof.

[0228] Because PAK6KD may crystallize in more than one crystal form, the structure coordinates of PAK6KD, or portions thereof, are particularly useful to solve the structure of those other crystal forms of PAK6KD. They may also be used to solve the structure of PAK6KD mutants, PAK6KD co-complexes, or of the crystalline form of any other protein with significant amino acid sequence homology to any functional domain of PAK6KD.

[0229] Homologs or mutants of PAK6KD may, for example, have an amino acid sequence homology to the Homo sapiens amino acid sequence of Fig. 2 of greater than 60%, more preferred proteins have a greater than 70% sequence homology, more preferred

proteins have a greater than 80% sequence homology, more preferred proteins have a greater than 90% sequence homology, and most preferred proteins have greater than 95% sequence homology. A protein domain, region, or binding pocket may have a level of amino acid sequence homology to the corresponding domain, region, or binding pocket amino acid sequence of Homo sapiens of Fig. 2 of greater than 60%, more preferred proteins have a greater than 70% sequence homology, more preferred proteins have a greater than 80% sequence homology, more preferred proteins have a greater than 90% sequence homology, and most preferred proteins have greater than 95% sequence homology. Percent homology may be determined using, for example, a PSI BLAST search, such as, but not limited to version 2.1.2 (Altschul, S.F., et al., Nuc. Acids Rec. 25:3389-3402, 1997).

[0230] One method that may be employed for this purpose is molecular replacement. In this method, the unknown crystal structure, whether it is another crystal form of PAK6KD, a PAK6KD mutant, or a PAK6KD co-complex, or the crystal of some other protein with significant amino acid sequence homology to any functional domain of PAK6KD, may be determined using phase information from the PAK6KD structure coordinates. This method may provide an accurate three-dimensional structure for the unknown protein in the new crystal more quickly and efficiently than attempting to determine such information *ab initio*. In addition, in accordance with this invention, PAK6KD mutants may be crystallized in co-complex with known PAK6KD inhibitors. The crystal structures of a series of such complexes may then be solved by molecular replacement and compared with that of wild-type PAK6KD. Potential sites for modification within the various binding pockets of the protein may thus be identified. A co-crystal may be obtained, for example, by soaking a crystalline form of a target protein in the presence of at least one ligand. Or, a co-crystal may be obtained, for example, by crystallizing a co-complex, by preparing a solution comprising a target protein and a ligand, and then following an appropriate crystallization method. The ligand may be present in the mother liquor or, if it is insoluble in the mother liquor, it may be dissolved, at the highest concentration possible, in DMSO, for example.

[0231] This information provides an additional tool for determining the most efficient binding interactions, for example, increased hydrophobic interactions, between PAK6KD and a chemical group or compound.

[0232] If an unknown crystal form has the same space group as and similar cell dimensions to the known PAK6KD crystal form, then the phases derived from the known crystal form may be directly applied to the unknown crystal form, and in turn, an electron density map for the unknown crystal form may be calculated. Difference electron density maps can then be used to examine the differences between the unknown crystal form and the known crystal form. A difference electron density map is a subtraction of one electron density map, *e.g.*, that derived from the known crystal form, from another electron density map, *e.g.*, that derived from the unknown crystal form. Therefore, all similar features of the two electron density maps are eliminated in the subtraction and only the differences between the two structures remain. For example, if the unknown crystal form is of a **PAK6KD** co-complex, then a difference electron density map between this map and the map derived from the native, uncomplexed crystal will ideally show only the electron density of the ligand. Similarly, if amino acid side chains have different conformations in the two crystal forms, then those differences will be highlighted by peaks (positive electron density) and valleys (negative electron density) in the difference electron density map, making the differences between the two crystal forms easy to detect. However, if the space groups and/or cell dimensions of the two crystal forms are different, then this approach will not work and molecular replacement must be used in order to derive phases for the unknown crystal form.

[0233] All of the complexes referred to above may be studied using well-known X-ray diffraction techniques and may be refined against data extending from about 500Å to at least 3.0Å or 1.5Å, until the refinement has converged to limits accepted by those skilled in the art, such as, but not limited to, R=0.2, Rfree=0.25. This may be determined using computer software, such as X-PLOR, CNX, or refmac (part of the CCP4 suite; Collaborative Computational Project, Number 4, "The CCP4 Suite: Programs for Protein Crystallography," Acta Cryst. D50, 760-63, 1994). See, *e.g.*, Blundell *et al* ., Protein Crystallography, Academic Press; Methods in Enzymology, Vols. 114 & 115, 1976; Wyckoff *et al.*, eds., Academic Press, 1985; Methods in Enzymology, Vols. 276 and 277 (Carter & Sweet, eds., Academic Press 1997); "Application of Maximum Likelihood Refinement" G. Murshudov, A.Vagin and E.Dodson, (1996) in the Refinement of Protein Structures, Proceedings of Daresbury Study Weekend; G.N. Murshudov, A.A.Vagin and E.J.Dodson, Acta Cryst. D53, 240-55, 1997; G.N.Murshudov, A.Lebedev, A.A.Vagin, K.S.Wilson and E.J.Dodson, Acta Cryst. Section D55, 247-55, 1999. See, *e.g.*, Blundell *et*

al., Protein Crystallography, Academic Press; Methods in Enzymology, Vols. 114 & 115, 1976; Wyckoff *et al.*, eds., Academic Press, Methods in Enzymology, Vols. 276 and 277, 1985 (Carter & Sweet, eds., Academic Press 1997). This information may thus be used to optimize known classes of PAK6 inhibitors, and more importantly, to design and synthesize novel classes of PAK6 inhibitors.

[0234] The structure coordinates of PAK6KD mutants will also facilitate the identification of related proteins or enzymes analogous to PAK6 in function, structure or both, thereby further leading to novel therapeutic modes for treating or preventing diseases or disorders in which PAK6 activity is implicated.

[0235] Subsets of the molecular structure coordinates may be used in any of the above methods. Particularly useful subsets of the coordinates include, but are not limited to, coordinates of single domains, coordinates of residues lining an active site or binding pocket, coordinates of residues that participate in important protein-protein contacts at an interface, and alpha-carbon coordinates. For example, the coordinates of one domain of a protein that contains the active site may be used to design inhibitors that bind to that site, even though the protein is fully described by a larger set of atomic coordinates. Therefore, a set of atomic coordinates that define the entire polypeptide chain, although useful for many applications, do not necessarily need to be used for the methods described herein.

EXAMPLES

Example 1: Determination of PAK6 Structure

[0236] The subsections below describe the production of a polypeptide comprising the Homo sapiens PAK6, and the preparation and characterization of diffraction quality crystals and heavy-atom derivative crystals.

Example 1.1: Preparation of PAK6 Crystals

[0237] Human liver cDNA is synthesized using a standard cDNA synthesis kit following the manufacturers' instructions. The template for the cDNA synthesis is mRNA isolated from JAR cells [ATCC HTB-144] using a standard RNA isolation kit. An open-reading frame for PAK6KD is amplified from the human liver cDNA by the polymerase chain reaction (PCR) using the following primers:

[0238] Forward primer: ACACATGAGCAGTTCAAGG

Reverse primer: CCTTTCGGTAGAGCTGGATC

The PCR product (873 base pairs expected) is electrophoresed on a 1% agarose gel in TBE buffer and the appropriate size band is excised from the gel and eluted using a standard gel extraction kit.

[0239] The eluted DNA is ligated for five minutes at room temperature with topoisomerase into pSGX6, previously digested with BamHI and HindIII. The vector pSGX6 is a topoisomerase-activated modified version of pET26b (Novagen, Madison, Wisconsin) wherein the coding sequence for smt3 (Genbank entry U27233) from amino acids 1 to 121 has been inserted between the NdeI and BamHI sites (Bernier-Villamor, V., et al., Cell 108:345-356, 2002). In addition, the pSGX6 vector contains a gene coding for lambda phosphatase.

[0240] The phosphatase co-expression plasmid was created by inserting the phosphatase gene from lambda bacteriophage into the above plasmid (Matsui T, et al., Biochem. Biophys. Res. Commun., 2001, 284:798-807). The phosphatase gene was amplified using PCR from template lambda bacteriophage DNA (HinDIII digest, New England Biolabs) using the following oligonucleotide primers:

Forward primer (PPfor): GCAGAGATCCGAATTCGAGCTCCGTCGACGGAT GGAGTGAAAGAGATGCGC

Reverse primer (PPrev): GGTGGTGGTGCTCGAGTGCGGCCGCAA GCTTTCATCATGCGCCTTCTCCCTGTAC

[0241] The PCR product (744 base pairs expected) was gel purified. The purified DNA and non-co-expression plasmid DNA were then digested with SacI and XhoI restriction enzymes. Both the digested plasmid and PCR product were then gel purified and ligated together for 8 hrs at 16° C with T4 DNA ligase and transformed into Top10 cells using standard procedures. The presence of the phosphatase gene in the co-expression plasmid was confirmed by sequencing. For standard molecular biology protocols followed here, see also, for example, the techniques described in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY, 2001, and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY, 1989.

[0242] The lambda phosphatase/PAK6KD co-expression plasmid contains both the PAK6KD and lambda phosphatase sequences under the control of the lac promoter, each with its own ribosome binding site. By cloning the phosphatase into the middle of the multiple cloning site, downstream of the target gene, convenient restriction sites are

available for subcloning the phosphatase into other plasmids. These sites include SacI, SalI and EcoRI between the kinase and phosphatase and HinDIII, NotI and XhoI downstream of the phosphatase.

[0243] The resulting sequence of the PAK6KD gene after being ligated into the vector, from the Shine-Dalgarno sequence through the stop site and the "original" HindIII, site is as follows: AAGGAGATATA CCATGGGCAGCA GCCATCATCATCATCA TCACAGCAGCGGCCT GGTGCCGCGCGGCAGCCATA TGGCTAGC[SMT3]TCC[ORF]. The PAK6KD expressed using this vector has an N-terminal methionine, then a 6 x His-tag followed by the smt3 fusion protein followed by the kinase domain of PAK6KD.

[0244] Plasmids containing ligated inserts are transformed into chemically competent TOP10 cells. Colonies are then screened for inserts in the correct orientation and small DNA amounts are purified using a "miniprep" procedure from 2 ml cultures, using a standard kit, following the manufacturer's instructions. For standard molecular biology protocols followed here, see also, for example, the techniques described in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY, 2001, and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY, 1989.

[0245] The miniprep DNA is transformed into BL21(DE3)-Codon+RIL cells and plated onto petri dishes containing LB agar with 30 μg/ml of kanamycin and 34 μg/ml of chloramphenicol. Isolated, single colonies are grown to mid-log phase and stored at –80°C in LB containing 15% glycerol.

[0246] The PAK6KD fusion protein is over expressed in *E. coli* in the presence of 60 mg/L selenomethionine as follows. Glycerol stocks are grown in LB (10g/L tryptone, 5g/L yeast extract, 10g/L NaCl) with 30 μg/ml kanamycin and 34 μg/ml chloramphenicol. The culture is grown to an OD600 of 0.6 to 1.0, then IPTG is added at a 0.4mM final concentration. The culture is allowed to ferment for 16hr at 20°C. The PAK6KD is purified as follows. Cells are collected by centrifugation, lysed in diluted cracking buffer (50 mM Tris HCl, pH 7.6, 0.1% Tween20), and centrifuged to remove cell debris. The soluble fraction is purified over an IMAC column charged with nickel (Pharmacia, Uppsala, Sweden), and eluted under native conditions with a gradient of 20mM to 500mM imidazole in 50mM Tris.pH7.8, 10mM methionine, 10% glycerol. Next, the PAK6KD

fusion protein is mixed with Ulp1 protease at a concentration of 1:10,000 in elution buffer and incubated overnight at 4°C (Bernier-Villamor, V., et al., Cell, 108:345-56, 2002); Mossessova, E., and Lima, C.D., Mol. Cell 5:865-76, 2000). The cleavage reaction takes place during dialysis against the IMAC starting buffer. The cleaved PAK6 fusion protein is passed over an IMAC column, charged with nickel, a second time. The cleaved PAK6 is recovered from the flowthrough, whereas the Smt-fusion partner, the uncleaved protein, and the His-tagged Ulp protease remained bound to the column. The cleaved PAK6KD fusion protein is then further purified by gel filtration using a Superdex 200 preparative grade column equilibrated in GF5 buffer (10mM HEPES, 10mM methionine, 500 mM NaCl, 5 mM DTT, and 10% glycerol). Fractions containing the purified PAK6KD kinase domain are pooled, concentrated to 8.5mg/ml, flash frozen and stored at -80°C. The protein obtained is 99% pure as judged by electrophoresis on SDS polyacrylamide gels. Mass spectroscopic analysis of the purified protein showed that it is predominantly singly phosphorylated.

[0247] For crystals of Homo sapiens PAK6 from which the molecular structure coordinates of the invention are obtained, it has been found that a sitting drop containing 1 µl of PAK6 polypeptide, 14 mg/ml, in 10 mM Hepes pH 7.5, 150 mM NaCl, 5mM DTT 10mM methionine, 1mM ADP, 2mM $MgCl_2$, 10% glycerol, and 1µl reservoir solution: 15 % (v/v) PEG 400, 200 mM sodium citrate dihydrate and 100 mM Tris-HCl, pH 8.5 in a sealed container containing 100µL reservoir solution, incubated at 21°C provides diffraction quality crystals. In one example, crystals first appeared within 24 hours, and matured within about 4 weeks.

[0248]Other examples of methods of obtaining a crystal comprise the steps of:(a) mixing a volume of a solution comprising the PAK6 with a volume of a reservoir solution comprising a precipitant, such as, for example, polyethylene glycol; and (b) incubating the mixture obtained in step (a) over the reservoir solution in a closed container, under conditions suitable for crystallization until the crystal forms. At least 10% (v/v) of PEG 400 is present in the reservoir solution. PEG 400 is, for example, present in a concentration up to about 20% (v/v). In another example, the concentration of PEG 400 is 15% (v/v). The concentration of Tris-HCl is, for example, at least 25mM. The concentration of Tris-HCl is, for example, up to about 200mM. In another example, the concentration of Tris-HCl is 100mM. The concentration of sodium citrate dihydrate is, for

example, at least 100mM. The concentration of sodium citrate dihydrate is, for example, up to about 300mM. In another example, the concentration of sodium citrate dihydrate is 200 mM. The reservoir solution has a pH of, for example, 8. The reservoir solution may, for example, have a pH up to about 9. In another example, the pH is about 8.5. The temperature is, for example, at least 4°C. The temperature may be, for example, up to about 30°C. In another example, the temperature is 21°C.

[0249] Those of ordinary skill in the art recognize that the drop and reservoir volumes may be varied within certain biophysical conditions and still allow crystallization.

Example 1.2: Crystal Diffraction Data Collection

[0250] The crystals are individually harvested from their trays and transferred to a cryoprotectant consisting of 80% reservoir solution plus 20% glycerol. After about 2 minutes the crystal is collected and transferred into liquid nitrogen. The crystals are transferred in liquid nitrogen to the Advanced Photon Source (Argonne National Laboratory) where a native data set is collected.

Example 1.3: Structure Determination

[0251] X-ray diffraction data are indexed and integrated using the program MOSFLM (Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-63, 1994; www.ccp4.ac.uk/main.html) and then merged using the program SCALA (Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-63, 1994; www.ccp4.ac.uk/main.html). The subsequent conversion of intensity data to structure factor amplitudes is carried out using the program TRUNCATE (Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-763, 1994; www.ccp4.ac.uk/main.html). An initial model was obtained by molecular replacement using a structure of PAK4, for example, a structure having the coordinates of a structure described in Publication No. US-2003-0229453-A1, published on December 11, 2003. as a search model using the program EPMR (Kissinger, CR, et al., *Acta Cryst.*, D55, 484-491, 1999). The initial protein model was built into the resulting map using the program XTALVIEW/XFIT (McRee, D.E. *J. Structural Biology,* 125:156-65, 1993; available from CCMS (San Diego Super Computer Center) CCMS-request@sdsc.edu.).

[0252] This model is refined using the program REFMAC (Brunger et al., Acta Cryst. D53, 240-55, 2000; Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-63, 1994; www.ccp4.ac.uk/main.html) with interactive refitting carried out using the program XTALVIEW/XFIT (McRee, D.E. *J. Structural Biology,* 125:156-65, 1993; available from CCMS (San Diego Super Computer Center) CCMS-request@sdsc.edu). The stereochemical quality of the atomic model is monitored using PROCHECK (Laskowski et al., *J. Appl. Cryst.* 26, 283-91, 1993) and WHATCHECK (Vriend, G., *J. Mol. Graph* 8:52-56, 1990; Hooft, R.W.W. et al., *Nature* 381:272, 1996) and the agreement of the model with the x-ray data is analyzed using SFCHECK (Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-63, 1994); www.ccp4.ac.uk/main.html).

Table 1 Data Collection Statistics

Space group Cell dimensions	P 21 21 21 a = 59.24 Å b = 66.72 Å c = 97.21 Å $\alpha = 90°$ $\beta = 90°$ $\gamma = 90°$
Wavelength λ	0.9794 Å
Overall Resolution limits	21.6 Å 1.46 Å
Number of reflections collected	241955
Number of unique reflections	64186
Overall Redundancy of data	3.6
Overall Completeness of data	98.4 %
Completeness of data in last data shell	90.9 %
Overall R_{SYM}	0.124
R_{SYM} in last resolved shell	1.793
Overall I/sigma(I)	6.4
I/sigma(I) in last shell	1.0

Table 2 Model Refinement Statistics

Model		
	Total number of atoms	2631
	Number of water molecules	240
	Temperature factor for all atoms	17.8 $Å^2$
	Matthews coefficient	2.61

	Corresponding solvent content	52.5 %
Refinement		
	Resolution limits	21.6 Å 1.46 Å
	Number of reflections used	64131
	with I > 1 sigma(I)	62900
	with I > 3 sigma(I)	32421
	Completeness	95 %
	R-factor for all reflections	0.196
	Correlation coefficient	0.955
	Number of reflections above 2 sigma(F) and resolution from 5.0 Å - high resolution limit	61215
	used to calculate Rworking	58117
	used to calculate Rfree	3098
	R-factor without free reflections	0.190
	R-factor for free reflections	0.224
	Error in coordinates estimated by Luzzati plot	0.187 Å
Validation		
	Phi-Psi core region	93.1 %
	Phi-Psi violations Residues in disallowed regions:	1
% bad contacts	Short contact distances	0
	RMSD from ideal bond length	0.021 Å
	RMSD from ideal bond angle	1.88 °

Example 1.4: Structure Analyses

[0253] Atomic superpositions are performed with MOE (available from Chemical Computing Group, Inc., Montreal, Quebec, Canada). Per residue solvent accessible surface calculations are done with GRASP (Nicholls *et al.*, "Protein folding and association: insights from the interfacial and thermodynamic properties of hydrocarbons," Proteins, 11:281-96, 1991). The electrostatic surface is calculated using a probe radius of 1.4Å.

Example 2: Use of PAK6KD Coordinates for Inhibitor Design

[0254] The coordinates of the present invention, including the coordinates of molecules comprising the binding pocket residues of Figure 4, as well as coordinates of homologs having a rmsd of the backbone atoms of preferably less than 1.5Å, more preferably less than 1.25Å, more preferably less than 1Å, more preferably less than 0.75Å, and more

preferably less than 0.5Å from the coordinates of Figure 4, are used to design compounds, including inhibitory compounds, that associate with PAK6, or homologs of PAK6. Such compounds may associate with PAK6 at the active site, in a binding pocket, in an accessory binding pocket, or in parts or all of both regions.

[0255] The process may be aided by using a computer comprising a computer readable database, wherein the database comprises coordinates of an active site, binding pocket, or accessory binding pocket of the present invention. The computer may be programmed, for example, with a set of machine-executable instructions, wherein the recorded instructions are capable of displaying a three-dimensional representation of PAK6, or portions thereof. The computer is used according to the methods described herein to design compounds that associate with PAK6, for example, at the active site or a binding pocket.

[0256] A chemical compound library is obtained. The library may be purchased from a publicly available source such as, for example, ChemBridge (San Diego, California, www.chembridge.com), Available Chemical Database, or Asinex (Moscow 123182, Russia, www.asinex.com). A filter is used to retain compounds in the library that satisfy the Lipinski rule of five, which states that compounds are likely to have good absorption and permeation in biological systems and are more likely to be successful drug candidates if they meet the following criteria: five or fewer hydrogen-bond donors, ten or fewer hydrogen-bond acceptors, molecular weight less than or equal to 500, and a calculated logP less than or equal to 5. (Lipinski, C.A., et al., Advanced Drug Delivery Reviews 23 3-25 (1996)).

[0257] This filter reduces the size of the compound library used to screen against the structure of the present invention. Docking programs described herein, such as, for example, DOCK, or GOLD, are used to identify compounds that bind to the active site and/or binding pocket. Compounds may be screened against more than one binding pocket of the protein structure, or more than one set of coordinates for the same protein, taking into account different molecular dynamic conformations of the protein. Consensus scoring may then be used to identify the compounds that are the best fit for the protein (Charifson, P.S. et al., J. Med. Chem. 42:5100-9 (1999)). Data obtained from more than one protein molecule structure may also be scored according to the methods described in Klingler et al., U.S. Utility Application, filed May 3, 2002, entitled "Computer Systems and Methods for Virtual Screening of Compounds." Compounds having the best fit are

then obtained from the producer of the chemical library, or synthesized, and used in binding assays and bioassays.

[0258] The coordinates of the present invention are also used to determine pharmacophores. These pharmacophores may be designed after reviewing results from the use of a docking program, to determine the shape of the PAK6 pharmacophore. Alternatively, programs such as GRID are used to calculate the properties of a pharmacophore. Once the pharmacophore is determined, it may be used to screen chemical libraries for compounds that fit within the pharmacophore.

[0259] The coordinates of the present invention are also used to identify substructures that interact with various portions of an active site or binding pocket of PAK6. Once a substructure, or set of substructures, is determined, it is used to screen a chemical library for compounds comprising the substructure or set of substructures. The identified compounds are then docked to, for example, the active site or binding pocket.

Example 3: Bioassay

[0260] The kinase assays may use various forms of PAK6KD and PAK6, including, for example, PAK6KD or the PAK6 molecule itself, or a portion thereof.

Binding Assay:

[0261] To measure the binding of a compound to PAK6 or PAK6KD, a test kit manufactured by Discoverx (Fremont, CA), ED-Staurosporine NSIP™ Enzyme Binding Assay Kit (see U.S. Patent No. 5,643,734) is used.

PAK4 Kinase assay:

[0262] To assay the kinase activity of PAK6 or PAK6KD, NIH 3T3 cells are transfected with either empty SRα expression vector or expression vectors containing HA-tagged PAK6 or PAK6KD. Cells are harvested in M2 buffer (Minden, A. *et al.*,*Science*, 266:1719-23, 1994) 48 h after transfection. Approximately 100 μg of cell extracts are mixed with anti-HA antibody and protein A-Sepharose and incubated 2 h to overnight at 4°C. The immune complexes are washed twice with M2 buffer and twice in 20 mM HEPES, pH 7.5, and incubated in a kinase buffer containing 20 μM ATP and 5 μCi of [γ-^{32}P]ATP together with either 5 μg of histone H4 or MBP (Boehringer Mannheim) or no substrate, at 30°C for 20 min. The reaction is stopped by boiling in 4× SDS loading buffer.

Proteins are resolved by SDS-PAGE, and substrate phosphorylation and autophosphorylation are visualized by autoradiography.

[0263] To measure autophosphorylation of purified PAK6 or PAK6KD, recombinant PAK6 or PAK6KD (2 μg bound to protein G-Sepharose conjugated with monoclonal glu-glu antibody) is washed once and incubated in 40 μl of kinase buffer (50 mM Tris-HCl, pH 7.5, 100 mM NaCl, 10 mM $MgCl_2$, 1 mM $MnCl_2$) with 2 μg of either Rac1 or Cdc42Hs, all previously loaded with GTP or GDP. The reaction is initiated by adding 10 μl of kinase buffer containing 50 μM ATP and 5 μCi of [γ-^{32}P]ATP and incubated for 20 min at 30°C. The reaction is stopped by adding 10 μl of 5× SDS-PAGE sample buffer and boiling for 5 min. Samples are applied to a 14% SDS-PAGE gel and exposed to film.

[0264] To measure modulation, activation, or inhibition of PAK6 or PAK6KD kinase activity, a test compound is added to the assay at a range of concentrations. Inhibitors may, for example, inhibit PAK6 or PAK6KD activity at an IC_{50} under 100 μM, for example under 10 μM, for example, under 1 μM, in the nanomolar range, or, for example, in the sub-nanomolar range.

Apoptosis Assay:

[0265] The ability of PAK6or PAK6KD to protect cells against apoptosis and delay caspase activation is measured as described (Gnesutta, N., et al., J. Biol. Chem., 276: 14414-19, 2001). NIH3T3 cells are stably transfected with either control, wild-type, or mutant PAK6 or PAK6KD vector (Qu, J. et al., Mol Cell Biol, 10: 3523-33, 2001). To estimate the level of apoptosis and survival of stably transfected cell lines, equal numbers of cells are seeded in growth medium in 3.5-, 6-, or 10-cm plates. After 48 hours, cells are assayed for apoptosis induction following treatments with UV irradiation, tumor necrosis factor alpha (TNFα), and serum deprivation. For UV irradiation, cells are washed twice in phosphate-buffered saline (PBS). After removal of the PBS, cells are exposed to 50 J/m^2 UV-light in a UV cross-linker (Fisher) followed by addition of fresh medium. For TNFα treatment, cells are washed once with fresh medium that was replaced by medium containing TNFα and cycloheximide (CHX) either alone or in combination at a concentration of 10 ng/ml and 10 μg/ml, respectively (CHX is used as a control to block the NF-kB-mediated survival pathway induced by TNFα). For serum deprivation experiments, cells are washed once with medium without serum, followed by addition of

fresh medium containing 0.1, 0.5, or 10% serum for 24 h. After stimulation, cells are collected at 1 h, 2 h, and 4 h intervals and fixed for flow cytometry analysis or used to prepare total cell extracts. To determine the percentage of cell death by flow cytometry analysis, cells with DNA content lower than the G_1 peak (sub-G_1) are considered to be apoptotic. Caspase-3-like activity is examined by Western blot analysis of the caspase-3 substrate PARP in equal amounts of cell lysate. Detection of the M_r 85,000 proteolytic product of PARPis used as an indication of caspase activity. To examine nuclear condensation, cells stained with Hoechst 33258 are analyzed by fluorescence microscopy. Cells that displayed condensed chromatin and blebbed nuclei are considered apoptotic. To determine the amount of cell death in each clone, apoptotic cells are counted in the same number of viewing fields. To determine survival rates, cells are seeded in 6-well plates and treated as described above. At the indicated time point, the medium is aspirated, and floating cells are removed by washing twice with PBS. Attached cells are collected and counted. The survival rate is expressed in percentage of surviving cells in treated cells compared with the untreated control.

[0266] To measure modulation, activation, or inhibition of PAK6KD, a test compound is added to the assay at a range of concentrations. Inhibitors may inhibit PAK6KD activity at an IC_{50} in the nanomolar range, and, for example, in the subnanomolar range.

[0267] To measure modulation, activation, or inhibition of PAK6KD, a test compound is added to the assay at a range of concentrations. Preferred inhibitors inhibit PAK6KD activity at an IC_{50} in the nanomolar range, or in the subnanomolar range.

Example 4: Formulation and Administration

[0268] Pharmaceutical compositions comprising PAK6 modulators, such as inhibitors, are useful, for example, for treating diseases and conditions that may be alleviated by modulation of PAK6. Pharmaceutical compositions containing PAK6 effectors may also be used to modify the activity of human homologs of PAK6.

[0269] In therapeutic and/or diagnostic applications, the compounds of the invention may be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20^{th} ed.) Lippincott, Williams & Wilkins (2000).

[0270] The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg from 0.5 to 100 mg, and from 1 to 50 mg per day, from 5 to 40 mg per day are examples of dosages that may be used. One example of a dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[0271] Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20^{th} ed.) Lippincott, Williams & Wilkins (2000). Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

[0272] Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained- low release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20^{th} ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

[0273] For injection, the agents of the invention may be formulated in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants

appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds may be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[0274] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0275] In addition to the active ingredients, these pharmaceutical compositions **may** contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which may be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

[0276] Pharmaceutical preparations for oral use may be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0277] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc,

polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0278] Pharmaceutical preparations that may be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[0279] The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those having skill in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the invention. References cited throughout this application are examples of the level of skill in the art and are hereby incorporated by reference herein in their entirety, whether previously specifically incorporated or not.

1. A PAK6or PAK6KD protein, or a functional PAK6KD protein subunit, in crystalline form.

2. The crystalline protein or functional protein subunit of claim 1, which is a heavy-atom derivative crystal.

3. The crystalline protein or functional protein subunit of claim 2, in which PAK6KD protein is a mutant.

4. The crystalline protein of claim 3, which is characterized by a set of structural coordinates that is substantially similar to the set of structural coordinates of Fig. 4.

5. A crystal comprising PAK6 protein and a ligand.

6. A method of identifying a ligand that binds PAK6 protein, comprising;

a) forming a co-crystal of a test ligand and PAK6 protein;

b) analyzing said co-crystal using X-ray crystallography; and

c) using said analysis to determine whether said test ligand binds PAK6 protein.

7. The method of claim 6 wherein said co-crystal is obtained by soaking a PAK6 protein crystal in a solution comprising said test ligand.

8. The method of claim 7 wherein said co-crystal is obtained by co-crystallizing PAK6 protein in the presence of said test ligand.

9. A machine-readable medium embedded with information that corresponds to a three-dimensional structural representation of a crystalline protein of claim 1.

10. The machine-readable medium of claim 9, embedded with the molecular structural coordinates of Fig. 4, or at least 50% of the coordinates thereof.

11. The machine-readable medium of claim 9, embedded with the molecular structural coordinates of Fig. 4, or at least 80% of the coordinates thereof.

12. The machine-readable medium of claim 9, embedded with the molecular structural coordinates of a protein molecule comprising a PAK6KD protein binding pocket, wherein said binding pocket comprises at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 having the structural coordinates of Fig. 4, or by the structural coordinates of a binding pocket homolog, wherein said the root mean square deviation of the backbone atoms of the amino acid residues of said binding pocket and said binding pocket homolog is less than 2.0Å.

13. The machine-readable medium of claim 12, wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

14. The machine-readable medium of claim 13, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

15. The machine-readable medium of claim 14, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

16. A method of electronically transmitting all or part of the information stored in the machine-readable medium of claim 9.

17. A method of producing a computer readable database comprising the three-dimensional molecular structural coordinates of a binding pocket of a PAK6KD protein, said method comprising

a) obtaining three-dimensional structural coordinates defining said protein or a binding pocket of said protein, from a crystal of said protein; and

b) introducing said structural coordinates into a computer to produce a database containing the molecular structural coordinates of said protein or said binding pocket.

18. The method of claim 17, wherein said binding pocket of said protein is part of a co-complex with at least one ligand.

19. The method of claim 17 wherein said binding pocket comprises amino acids Val, Lys, Glu, Val, Met, Glu, Leu, Leu, Ser, and Asp.

20. The method of claim 19 wherein said computer is capable of utilizing or displaying a three-dimensional molecular structure comprising said binding pocket using said structural coordinates.

21. The method of claim 19 wherein said binding pocket further comprises amino acids corresponding to Gly, Glu, Gly, Ser, Thr, Gly, Ile, Ala, Met, Phe, and Asp.

22. The method of claim 21 wherein said binding pocket further comprises amino acids corresponding to Leu, Gln, Arg, Leu, Gln, Gly, Gly, Ala, Asp, Gly, Phe, Arg, and Lys.

23. The method of claim 17 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

24. The method of claim 23 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

25. The method of claim 24, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

26. The method of claim 25, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

27. The method of claim 17, wherein said binding pocket comprises an active site.

28. A computer readable database produced by claim 17.

29. A method comprising electronic transmission of all or part of the computer readable database produced by claim 17.

30. A method of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of a PAK6KD protein, said method comprising

a) introducing into a computer program a computer readable database produced by claim 17;

b) generating a three-dimensional representation of a binding pocket of said PAK6KD protein in said computer program;

c) superimposing a three-dimensional model of at least one binding test compound on said representation of the binding pocket;

d) assessing whether said test compound model fits spatially into the binding pocket of said PAK6KD protein; and

e) storing a representation of a compound that fits into the binding pocket into a computer readable database.

31. The method of claim 30 wherein in e), said representation is stored in the database produced by claim 17.

32. The method of claim 30, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional molecular structural coordinates of the compound.

33. The method of claim 30, wherein said generating of a three-dimensional representation of the binding pocket comprises use of structural coordinates having a root mean square deviation of the backbone atoms of the amino acid residues of said binding pocket of less than 2.0Å from the structural coordinates of the corresponding residues according to Fig. 4.

34. The method of claim 30, wherein said at least one binding test compound is selected by a method selected from i) selecting a compound from a small molecule database, (ii) modifying a known inhibitor, substrate, reaction intermediate, or reaction product, or a portion thereof, of PAK6KD, (iii) assembling chemical fragments or groups into a compound, and (iv) de novo ligand design of said compound.

35. The method of claim 30, wherein said assessing of whether a test compound model fits is by docking the model to said representation of said PAK6KD binding pocket and/or performing energy minimization.

36. The method of claim 30 further comprising

f) preparing a binding test compound represented in said computer readable database;

g) contacting said compound in a binding assay with a protein comprising said PAK6KD protein binding pocket;

h) determining whether said test compound binds to said protein in said assay; and

i) introducing a representation of a compound that binds to said protein in said assay into a computer readable database.

37. The method of claim 35 wherein in i), said representation is stored in said database.

38. The method of claim 35, wherein said representation is selected from the group consisting of the compound's name, a chemical formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional molecular structural coordinates of the compound.

39. A method of producing a computer readable database comprising a representation of a binding pocket of a PAK6KD protein in a co-crystal with a compound, said method comprising

a) preparing a binding test compound represented in a computer readable database produced by claim 30;

b) forming a co-crystal of said compound with a protein comprising a binding pocket of a PAK6KD protein;

c) obtaining the structural coordinates of said binding pocket in said co-crystal; and

d) introducing the structural coordinates of said binding pocket or said co-crystal into a computer-readable database.

40. The method of claim 39, further comprising introducing the structural coordinates of said compound in said co-crystal into said database.

41. The method of claim 30 wherein said binding pocket comprises amino acids Val, Lys, Glu, Val, Met, Glu, Leu, Leu, Ser, and Asp.

42. The method of claim 41 wherein said computer is capable of utilizing or displaying a three-dimensional molecular structure of said binding pocket using said structural coordinates.

43. The method of claim 42 wherein said binding pocket further comprises amino acids corresponding to Gly, Glu, Gly, Ser, Thr, Gly, Ile, Ala, Met, Phe, and Asp.

44. The method of claim 43 wherein said binding pocket further comprises amino acids corresponding to Leu, Gln, Arg, Leu, Gln, Gly, Gly, Ala, Asp, Gly, Phe, Arg, and Lys.

45. The method of claim 30 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

46. The method of claim 45 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

47. The method of claim 46, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

48. The method of claim 47, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

49. The method of claim 30, wherein said binding pocket comprises an active site.

50. A computer readable database produced by claim 30.

51. A method comprising electronic transmission of all or part of the computer readable database produced using the method of claim 17.

52. A method of modulating PAK6KD protein activity comprising contacting said PAK6KD with a compound, wherein said compound is represented in a database produced by the method of claim 30.

53. A method of producing a compound comprising a three-dimensional molecular structure represented by the coordinates contained in a computer readable database produced by claim 30 comprising synthesizing said compound wherein said compound binds in a binding pocket of PAK6KD protein.

54. A method of modulating PAK6KD protein activity, comprising contacting said PAK6KD protein with a compound produced by claim 53.

55. A method of identifying an activator or inhibitor of a protein that comprises a PAK6KD active site or binding pocket, comprising

a) producing a compound according to claim 53;

b) contacting said compound with a protein that comprises a PAK6KD active site or binding pocket; and

c) determining whether the potential modulator activates or inhibits the activity of said protein.

56. A method of producing an activator or inhibitor identified by claim 55.

57. A method of producing a computer readable database comprising a representation of a compound rationally designed to be capable of binding a binding pocket of a PAK6KD protein, said method comprising

a) introducing into a computer program a computer readable database produced by claim 17;

b) generating a three-dimensional representation of the protein or a binding pocket of said PAK6KD protein in said computer program;

c) designing a three-dimensional model of a compound that forms non-covalent bonds with amino acids of a binding pocket of said representation; and

d) storing a representation of said compound into a computer readable database.

58. The method of claim 58, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional structural coordinates of the compound.

59. The method of claim 57 further comprising

e) preparing a binding test compound comprising a three-dimensional molecular structure represented by the coordinates contained in said computer readable database;

f) contacting said compound in a binding assay with a protein comprising said binding pocket of a PAK6KD protein;

g) determining whether said test compound binds to said protein in said assay; and

h) introducing a representation of a compound that binds to said protein in said assay into a computer-readable database.

60. The method of claim 59, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional structural coordinates of the compound.

61. A method of producing a computer readable database comprising a representation of a binding pocket of a PAK6KD protein in a co-crystal with a compound rationally designed to be capable of binding said binding pocket, said method comprising

a) preparing a binding test compound represented in a computer readable database produced by claim 57;

b) forming a co-crystal of said compound with a protein comprising a binding pocket of a PAK6KD protein;

c) obtaining the structural coordinates of said binding pocket in said co-crystal; and

d) introducing the structural coordinates of said binding pocket or said co-crystal into a computer-readable database.

62. The method of claim 61, further comprising introducing the structural coordinates of said compound in said co-crystal into said database.

63. The method of claim 57 wherein said binding pocket comprises amino acids Val, Lys, Glu, Val, Met, Glu, Leu, Leu, Ser, and Asp.

64. The method of claim 63 wherein said binding pocket further comprises amino acids corresponding to Gly, Glu, Gly, Ser, Thr, Gly, Ile, Ala, Met, Phe, and Asp.

65. The method of claim 64 wherein said binding pocket further comprises amino acids corresponding to Leu, Gln, Arg, Leu, Gln, Gly, Gly, Ala, Asp, Gly, Phe, Arg, and Lys.

66. The method of claim 57 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

67. The method of claim 66 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

68. The method of claim 67, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

69. The method of claim 68, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

70. The method of claim 57, wherein said binding pocket comprises an active site.

71. A computer readable database produced using the method of claim 57.

72 A method comprising electronic transmission of all or part of the computer readable database produced using the method of claim 57.

73 A method of producing a computer readable database comprising structural information about a molecule or a molecular complex of unknown structure comprising:

a) generating an x-ray diffraction pattern from a crystallized form of said molecule or molecular complex;

b) using a molecular replacement method to interpret the structure of said molecule; wherein said molecular replacement method uses the structural coordinates of a crystalline protein of claim 1, or the structural coordinates of Fig. 4, or a subset thereof comprising a binding pocket, the structural coordinates of a binding pocket of Fig. 4, or structural coordinates having a root mean square deviation for the alpha-carbon atoms of said structural coordinates of less than 2.0Å; and

c) storing the coordinates of the resulting structure in a computer readable database.

74. The method of claim 73 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

75. The method of claim 74 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

76. The method of claim 75, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

77. The method of claim 76, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

78. The method of claim 73, wherein said binding pocket comprises an active site.

79. A computer readable database produced using the method of claim 73.

80. A method comprising electronic transmission of all or part of the computer readable database produced by claim 73.

81. A method for homology modeling the structure of a PAK6KD protein homolog comprising:

a) aligning the amino acid sequence of a PAK6KD protein homolog with an amino acid sequence of PAK6KD protein;

b) incorporating the sequence of the PAK6KD protein homolog into a model of the structure of PAK6KD protein, wherein said model has the same structural coordinates as the structural coordinates of a crystalline protein of claim 1, or the structural coordinates of Fig. 4, or wherein the structural coordinates of said model's alpha-carbon atoms have a root mean square deviation from the structural coordinates of Fig. 4, of less than 2.0Å to yield a preliminary model of said homolog;

c) subjecting the preliminary model to energy minimization to yield an energy minimized model; and

d) remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of said homolog.

82. A method for identifying a compound that binds PAK6KD protein comprising:

a) providing a computer modeling program with a set of structural coordinates or a three dimensional conformation for a molecule that comprises a binding pocket of a crystalline protein of claim 1, or a homolog thereof;

b) providing a said computer modeling program with a set of structural coordinates of a chemical entity;

c) using said computer modeling program to evaluate the potential binding or interfering interactions between the chemical entity and said binding pocket; and

d) determining whether said chemical entity potentially binds to or interferes with said protein or homolog.

83. The method of claim 82 further comprising the steps of:

e) computationally modifying the structural coordinates or three dimensional conformation of said chemical entity to improve the likelihood of binding to said binding pocket; and

b) determining whether said modified chemical entity potentially binds to or interferes with said protein or homolog.

84. The method of claim 82 wherein determining whether the chemical entity potentially binds to said molecule comprises performing a fitting operation between the chemical entity and a binding pocket of the protein or homolog; and computationally analyzing the results of the fitting operation to quantify the association between, or the interference with, the chemical entity and the binding pocket.

85. The method of claim 82 wherein a library of structural coordinates of chemical entities is used to identify a compound that binds.

86. A method for designing a compound that binds PAK6KD protein comprising:

a) providing a computer modeling program with a set of structural coordinates, or a three dimensional conformation derived therefrom, for a molecule that comprises a binding pocket comprising the structural coordinates of a binding pocket of a crystalline protein of claim 1, or a homolog thereof;

b) computationally building a chemical entity represented by set of structural coordinates; and

c) determining whether the chemical entity is expected to bind to said molecule.

87. The method of claim 86, wherein determining whether the chemical entity potentially binds to said molecule comprises performing a fitting operation between the chemical entity and a binding pocket of the molecule; and

computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

88. The method of claim 86 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

89. The method of claim 88 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

90. The method of claim 89, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

91. The method of claim 90, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

92. The method of claim 86, wherein said binding pocket comprises an active site.

93. A method of producing a mutant PAK6KD protein, having an altered property relative to PAK6KD protein, comprising,

a) constructing a three-dimensional structure of PAK6KD protein having structural coordinates selected from the group consisting of the structural coordinates of a crystalline protein of claim 1, the structural coordinates of Fig. 4, and the structural coordinates of a protein having a root mean square deviation of the alpha carbon atoms of said protein of less than 2.0 Å when compared to the structural coordinates of Fig. 4;

b) using modeling methods to identify in the three-dimensional structure at least one structural part of the PAK6KD protein molecule wherein an alteration in said structural part is predicted to result in said altered property;

c) providing a nucleic acid molecule coding for a PAK6KD mutant protein having a modified sequence that encodes a deletion, insertion, or substitution of one or more amino acids at a position corresponding to said structural part; and

d) expressing said nucleic acid molecule to produce said mutant;

wherein said mutant has at least one altered property relative to the parent.

94. A method of producing a mutant PAK6KD protein, having an altered property relative to PAK6KD protein, comprising,

a) constructing a three-dimensional structure of a molecule comprising a binding pocket, wherein said binding pocket comprises at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530 , Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 having the structural coordinates of a crystalline protein of claim 1, the structural coordinates of Fig. 4, or the structural coordinates of a binding pocket homolog, wherein said the root mean square deviation of the backbone atoms of the amino acid residues of said binding pocket and said binding pocket homolog is less than 2.0Å;

b) using modeling methods to identify in the three-dimensional structure at least one portion of said binding pocket wherein an alteration in said portion is predicted to result in said altered property;

c) providing a nucleic acid molecule coding for a mutant PAK6KD protein having a modified sequence that encodes a deletion, insertion, or substitution of one or more amino acids at a position corresponding to said portion; and

d) expressing said nucleic acid molecule to produce said mutant;

wherein said mutant has at least one altered property relative to the parent.

95. A method of producing a computer readable database containing the three-dimensional molecular structural coordinates of a compound capable of binding the active site or binding pocket of a protein molecule, said method comprising

a) introducing into a computer program a computer readable database produced by claim 17;

b) generating a three-dimensional representation of the active site or binding pocket of said PAK6KD protein in said computer program;

c) superimposing a three-dimensional model of at least one binding test compound on said representation of the active site or binding pocket;

d) assessing whether said test compound model fits spatially into the active site or binding pocket of said PAK6KD protein;

e) assessing whether a compound that fits will fit a three-dimensional model of another protein, the structural coordinates of which are also introduced into said computer program and used to generate a three-dimensional representation of the other protein; and

f) storing the three-dimensional molecular structural coordinates of a model that does not fit the other protein into a computer readable database.

96. A method for determining whether a compound binds PAK6KD protein, comprising,

a) providing a computer modeling program with a set of structural coordinates or a three dimensional conformation for a molecule that comprises a binding pocket of a crystalline protein of claim 1, PAK6KD protein, or a homolog thereof;

b) providing a said computer modeling program with a set of structural coordinates of a chemical entity;

c) using said computer modeling program to evaluate the potential binding or interfering interactions between the chemical entity and said binding pocket; and

d) determining whether said chemical entity potentially binds to or interferes with said protein or homolog.

97. A method of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of a PAK6KD protein, said method comprising,

a) introducing into a computer program a computer readable database produced by claim 17;

b) determining a pharmacophore that fits within said binding pocket;

c) computationally screening a plurality of compounds to determine which compound(s) or portion(s) thereof fit said pharmacophore; and

d) storing a representation of said compound(s) or portion(s) thereof into a computer readable database.

98. The method of claim 97, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional molecular structural coordinates of the compound.

99. The method of claim 97 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

100. The method of claim 99 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

101. The method of claim 100, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

102. The method of claim 101, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

103. The method of claim 97, wherein said binding pocket comprises an active site.

104. A computer readable database produced using the method of claim 97.

105. A method comprising electronic transmission of all or part of the computer readable database produced using the method of claim 97.

106. A method of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of a PAK6KD protein, said method comprising

a) introducing into a computer program a computer readable database produced by claim 17;

b) determining a chemical moiety that interacts with said binding pocket;

c) computationally screening a plurality of compounds to determine which compound(s)comprise said moiety as a substructure of said compound(s); and

d) storing a representation of said compound(s) that comprise said substructure into a computer readable database.

107. The method of claim 106, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional molecular structural coordinates of the compound.

108. The method of claim 106 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

109. The method of claim 108 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

110. The method of claim 109, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

111. The method of claim 110, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

112. The method of claim 106, wherein said binding pocket comprises an active site.

113. A computer readable database produced using the method of claim 106.

114. A method comprising electronic transmission of all or part of the computer readable database produced using the method of claim 106.

115. Crystallizable PAK6 protein.

116. A method of purifying PAK6 protein linked to a histidine tag comprising:

a) obtaining a translation vector comprising a coding sequence for PAK6 protein, linked to a histidine tag;

b) performing size exclusion chromatography; and

c) performing nickel chelating column chromatography.

117. Purified PAK6KD polypeptide.

118. The method of claim 117 wherein said polypeptide is 98% pure.

119. The method of claim 117 wherein said polypeptide is unphosphorylated.

120. A method of purifying PAK6 polypeptide, comprising
expressing PAK6 in insect cells;
obtaining a soluble protein fraction from said insect cells;
using a two column chromatograph procedure to obtain purified PAK6.

121. An insect cell capable of expressing PAK6.

122. The insect cell of claim 121, wherein said insect cell comprises a vector, wherein said vector comprises a nucleic acid sequence coding for PAK6.

123. The use of the methods of any of claims 6-122 for drug discovery.

ABSTRACT

The present invention provides machine readable media embedded with the three-dimensional molecular structure coordinates of PAK6KD and subsets thereof, including binding pockets, methods of using the structure to identify and design affecters, including inhibitors and activator, mutants of PAK6KD, PAK6KD crystals and compounds and compositions that affect PAK6 activity.

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FIG. 1

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SEQRES   1 A  295  SER LEU THR HIS GLU GLN PHE LYS ALA ALA LEU ARG MET
SEQRES   2 A  295  VAL VAL ASP GLN GLY ASP PRO ARG LEU LEU LEU ASP SER
SEQRES   3 A  295  TYR VAL LYS ILE GLY GLU GLY SER THR GLY ILE VAL CYS
SEQRES   4 A  295  LEU ALA ARG GLU LYS HIS SER GLY ARG GLN VAL ALA VAL
SEQRES   5 A  295  LYS MET MET ASP LEU ARG LYS GLN GLN ARG ARG GLU LEU
SEQRES   6 A  295  LEU PHE ASN GLU VAL VAL ILE MET ARG ASP TYR GLN HIS
SEQRES   7 A  295  PHE ASN VAL VAL GLU MET TYR LYS SER TYR LEU VAL GLY
SEQRES   8 A  295  GLU GLU LEU TRP VAL LEU MET GLU PHE LEU GLN GLY GLY
SEQRES   9 A  295  ALA LEU THR ASP ILE VAL SER GLN VAL ARG LEU ASN GLU
SEQRES  10 A  295  GLU GLN ILE ALA THR VAL CYS GLU ALA VAL LEU GLN ALA
SEQRES  11 A  295  LEU ALA TYR LEU HIS ALA GLN GLY VAL ILE HIS ARG ASP
SEQRES  12 A  295  ILE LYS SER ASP SER ILE LEU LEU THR LEU ASP GLY ARG
SEQRES  13 A  295  VAL LYS LEU SER ASP PHE GLY PHE CYS ALA GLN ILE SER
SEQRES  14 A  295  LYS ASP VAL PRO LYS ARG LYS SEP LEU VAL GLY THR PRO
SEQRES  15 A  295  TYR TRP MET ALA PRO GLU VAL ILE SER ARG SER LEU TYR
SEQRES  16 A  295  ALA THR GLU VAL ASP ILE TRP SER LEU GLY ILE MET VAL
SEQRES  17 A  295  ILE GLU MET VAL ASP GLY GLU PRO PRO TYR PHE SER ASP
SEQRES  18 A  295  SER PRO VAL GLN ALA MET LYS ARG LEU ARG ASP SER PRO
SEQRES  19 A  295  PRO PRO LYS LEU LYS ASN SER HIS LYS VAL SER PRO VAL
SEQRES  20 A  295  LEU ARG ASP PHE LEU GLU ARG MET LEU VAL ARG ASP PRO
SEQRES  21 A  295  GLN GLU ARG ALA THR ALA GLN GLU LEU LEU ASP HIS PRO
SEQRES  22 A  295  PHE LEU LEU GLN THR GLY LEU PRO GLU CYS LEU VAL PRO
SEQRES  23 A  295  LEU ILE GLN LEU TYR ARG LYS GLU GLY
```

FIGURE 2

FIG. 3

CRYST1 59.242 66.718 97.213 90.00 90.00 90.00 P 21 21 21 4

	Atom Type		Residue		#	X	Y	Z	OCC	B	Atom
ATOM	1	N	SER	A	1	4.255	69.582	-7.189	1.00	37.48	N
ATOM	2	CA	SER	A	1	5.538	68.936	-6.810	1.00	37.14	C
ATOM	3	C	SER	A	1	6.478	69.003	-8.019	1.00	34.33	C
ATOM	4	O	SER	A	1	6.045	69.367	-9.121	1.00	34.04	O
ATOM	5	CB	SER	A	1	5.282	67.476	-6.416	1.00	38.61	C
ATOM	6	OG	SER	A	1	4.772	66.768	-7.542	1.00	42.89	O
ATOM	7	N	LEU	A	2	7.741	68.627	-7.804	1.00	29.21	N
ATOM	8	CA	LEU	A	2	8.735	68.581	-8.863	1.00	24.19	C
ATOM	9	C	LEU	A	2	8.369	67.552	-9.936	1.00	23.79	C
ATOM	10	O	LEU	A	2	7.887	66.435	-9.649	1.00	22.85	O
ATOM	11	CB	LEU	A	2	10.121	68.278	-8.235	1.00	23.41	C
ATOM	12	CG	LEU	A	2	10.709	69.380	-7.331	1.00	23.54	C
ATOM	13	CD1	LEU	A	2	12.145	69.111	-6.891	1.00	25.23	C
ATOM	14	CD2	LEU	A	2	10.630	70.780	-7.975	1.00	25.66	C
ATOM	15	N	THR	A	3	8.628	67.866	-11.193	1.00	20.07	N
ATOM	16	CA	THR	A	3	8.543	66.817	-12.192	1.00	18.28	C
ATOM	17	C	THR	A	3	9.664	65.811	-11.944	1.00	16.21	C
ATOM	18	O	THR	A	3	10.598	66.072	-11.146	1.00	17.46	O
ATOM	19	CB	THR	A	3	8.714	67.404	-13.617	1.00	18.77	C
ATOM	20	OG1	THR	A	3	10.037	67.979	-13.747	1.00	19.31	O
ATOM	21	CG2	THR	A	3	7.741	68.587	-13.828	1.00	19.26	C
ATOM	22	N	HIS	A	4	9.598	64.692	-12.677	1.00	15.92	N
ATOM	23	CA	HIS	A	4	10.674	63.697	-12.624	1.00	15.47	C
ATOM	24	C	HIS	A	4	12.040	64.304	-12.952	1.00	15.13	C
ATOM	25	O	HIS	A	4	13.034	64.106	-12.229	1.00	14.28	O
ATOM	26	CB	HIS	A	4	10.328	62.527	-13.538	1.00	16.70	C
ATOM	27	CG	HIS	A	4	11.405	61.499	-13.646	1.00	18.74	C
ATOM	28	ND1	HIS	A	4	11.867	60.786	-12.553	1.00	16.57	N
ATOM	29	CE1	HIS	A	4	12.819	59.947	-12.952	1.00	18.77	C
ATOM	30	NE2	HIS	A	4	13.016	60.122	-14.260	1.00	18.88	N
ATOM	31	CD2	HIS	A	4	12.136	61.072	-14.713	1.00	16.88	C
ATOM	32	N	GLU	A	5	12.096	65.079	-14.051	1.00	15.64	N
ATOM	33	CA	GLU	A	5	13.341	65.723	-14.452	1.00	14.44	C
ATOM	34	C	GLU	A	5	13.880	66.698	-13.398	1.00	13.99	C
ATOM	35	O	GLU	A	5	15.072	66.706	-13.114	1.00	14.25	O
ATOM	36	CB	GLU	A	5	13.183	66.393	-15.842	1.00	17.22	C
ATOM	37	CG	GLU	A	5	12.961	65.370	-16.986	1.00	19.67	C
ATOM	38	N	GLN	A	6	13.002	67.519	-12.837	1.00	14.17	N
ATOM	39	CA	GLN	A	6	13.372	68.446	-11.773	1.00	12.69	C
ATOM	40	C	GLN	A	6	13.851	67.682	-10.527	1.00	12.96	C
ATOM	41	O	GLN	A	6	14.795	68.122	-9.890	1.00	13.85	O
ATOM	42	CB	GLN	A	6	12.206	69.356	-11.355	1.00	14.71	C
ATOM	43	CG	GLN	A	6	11.889	70.403	-12.402	1.00	14.71	C
ATOM	44	CD	GLN	A	6	10.736	71.234	-11.957	1.00	18.09	C
ATOM	45	OE1	GLN	A	6	9.704	70.691	-11.563	1.00	19.71	O
ATOM	46	NE2	GLN	A	6	10.889	72.540	-11.996	1.00	18.73	N
ATOM	47	N	PHE	A	7	13.149	66.594	-10.180	1.00	13.18	N
ATOM	48	CA	PHE	A	7	13.576	65.856	-9.002	1.00	13.46	C
ATOM	49	C	PHE	A	7	14.967	65.228	-9.179	1.00	12.12	C
ATOM	50	O	PHE	A	7	15.800	65.298	-8.270	1.00	12.52	O
ATOM	51	CB	PHE	A	7	12.525	64.820	-8.607	1.00	14.09	C
ATOM	52	CG	PHE	A	7	12.837	64.178	-7.289	1.00	14.22	C
ATOM	53	CD1	PHE	A	7	13.240	62.870	-7.258	1.00	18.17	C
ATOM	54	CE1	PHE	A	7	13.556	62.242	-6.027	1.00	20.16	C
ATOM	55	CZ	PHE	A	7	13.562	63.010	-4.858	1.00	18.29	C

FIGURE 4A

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ATOM     56  CE2 PHE A   7      13.169  64.352  -4.903  1.00 15.59           C
ATOM     57  CD2 PHE A   7      12.829  64.928  -6.129  1.00 15.24           C
ATOM     58  N   LYS A   8      15.242  64.632 -10.344  1.00 12.05           N
ATOM     59  CA  LYS A   8      16.615  64.100 -10.599  1.00 13.93           C
ATOM     60  C   LYS A   8      17.658  65.192 -10.445  1.00 12.47           C
ATOM     61  O   LYS A   8      18.748  64.950  -9.871  1.00 13.87           O
ATOM     62  CB  LYS A   8      16.779  63.491 -12.012  1.00 14.57           C
ATOM     63  CG  LYS A   8      16.029  62.172 -12.163  1.00 14.30           C
ATOM     64  CD  LYS A   8      16.429  61.472 -13.467  1.00 18.88           C
ATOM     65  CE  LYS A   8      15.814  62.234 -14.607  1.00 20.22           C
ATOM     66  NZ  LYS A   8      16.119  61.582 -15.919  1.00 20.03           N
ATOM     67  N   ALA A   9      17.367  66.394 -10.951  1.00 14.03           N
ATOM     68  CA  ALA A   9      18.346  67.485 -10.827  1.00 14.54           C
ATOM     69  C   ALA A   9      18.595  67.897  -9.402  1.00 15.46           C
ATOM     70  O   ALA A   9      19.741  68.188  -9.031  1.00 16.59           O
ATOM     71  CB  ALA A   9      17.894  68.693 -11.706  1.00 15.19           C
ATOM     72  N   ALA A  10      17.533  67.868  -8.585  1.00 14.46           N
ATOM     73  CA  ALA A  10      17.643  68.204  -7.167  1.00 13.59           C
ATOM     74  C   ALA A  10      18.505  67.108  -6.493  1.00 13.88           C
ATOM     75  O   ALA A  10      19.410  67.403  -5.714  1.00 14.66           O
ATOM     76  CB  ALA A  10      16.272  68.226  -6.529  1.00 16.88           C
ATOM     77  N   LEU A  11      18.222  65.842  -6.794  1.00 13.13           N
ATOM     78  CA  LEU A  11      19.023  64.740  -6.182  1.00 12.29           C
ATOM     79  C   LEU A  11      20.467  64.798  -6.537  1.00 15.09           C
ATOM     80  O   LEU A  11      21.349  64.449  -5.740  1.00 12.86           O
ATOM     81  CB  LEU A  11      18.493  63.381  -6.622  1.00 14.59           C
ATOM     82  CG  LEU A  11      17.316  62.889  -5.873  1.00 17.11           C
ATOM     83  CD1 LEU A  11      16.871  61.586  -6.587  1.00 16.74           C
ATOM     84  CD2 LEU A  11      17.706  62.644  -4.346  1.00 14.63           C
ATOM     85  N   ARG A  12      20.743  65.234  -7.779  1.00 15.23           N
ATOM     86  CA  ARG A  12      22.132  65.250  -8.197  1.00 19.00           C
ATOM     87  C   ARG A  12      22.987  66.119  -7.326  1.00 19.99           C
ATOM     88  O   ARG A  12      24.199  65.909  -7.222  1.00 23.19           O
ATOM     89  CB  ARG A  12      22.245  65.740  -9.640  1.00 20.72           C
ATOM     90  CG BARG A  12      21.680  64.776 -10.661  0.25 18.88           C
ATOM     91  CG AARG A  12      22.271  64.657 -10.588  0.75 21.37           C
ATOM     92  CD BARG A  12      22.457  64.703 -12.006  0.25 20.36           C
ATOM     93  CD AARG A  12      22.567  65.121 -12.042  0.75 20.08           C
ATOM     94  NE BARG A  12      22.285  63.396 -12.639  0.25 20.74           N
ATOM     95  NE AARG A  12      21.810  64.220 -12.856  0.75 16.51           N
ATOM     96  CZ BARG A  12      23.195  62.422 -12.664  0.25 19.97           C
ATOM     97  CZ AARG A  12      20.687  64.526 -13.470  0.75 14.33           C
ATOM     98  NH1BARG A  12      24.396  62.594 -12.129  0.25 20.48           N
ATOM     99  NH1AARG A  12      20.244  65.775 -13.471  0.75 14.60           N
ATOM    100  NH2BARG A  12      22.903  61.277 -13.256  0.25 20.12           N
ATOM    101  NH2AARG A  12      20.037  63.567 -14.086  0.75 14.64           N
ATOM    102  N   MET A  13      22.391  67.107  -6.705  1.00 21.69           N
ATOM    103  CA  MET A  13      23.132  67.991  -5.819  1.00 25.09           C
ATOM    104  C   MET A  13      23.521  67.344  -4.476  1.00 23.34           C
ATOM    105  O   MET A  13      24.463  67.797  -3.844  1.00 24.70           O
ATOM    106  CB  MET A  13      22.332  69.270  -5.545  1.00 27.66           C
ATOM    107  CG  MET A  13      21.864  70.008  -6.805  1.00 35.01           C
ATOM    108  SD  MET A  13      23.223  70.327  -7.952  1.00 49.17           S
ATOM    109  CE  MET A  13      24.051  71.787  -7.093  1.00 49.02           C
ATOM    110  N   VAL A  14      22.823  66.277  -4.068  1.00 17.63           N
ATOM    111  CA  VAL A  14      22.997  65.734  -2.731  1.00 17.18           C
ATOM    112  C   VAL A  14      23.452  64.289  -2.628  1.00 16.20           C
ATOM    113  O   VAL A  14      23.824  63.812  -1.533  1.00 17.02           O
ATOM    114  CB  VAL A  14      21.669  65.947  -1.894  1.00 17.40           C
ATOM    115  CG1 VAL A  14      21.251  67.444  -1.891  1.00 20.61           C
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FIGURE 4B

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ATOM    116  CG2 VAL A  14      20.521  65.056  -2.439  1.00 18.92           C
ATOM    117  N   VAL A  15      23.375  63.540  -3.743  1.00 14.22           N
ATOM    118  CA  VAL A  15      23.815  62.157  -3.643  1.00 13.93           C
ATOM    119  C   VAL A  15      25.342  62.069  -3.693  1.00 13.29           C
ATOM    120  O   VAL A  15      26.038  63.039  -4.027  1.00 14.68           O
ATOM    121  CB  VAL A  15      23.249  61.270  -4.760  1.00 14.80           C
ATOM    122  CG1 VAL A  15      21.744  61.193  -4.633  1.00 13.87           C
ATOM    123  CG2 VAL A  15      23.685  61.804  -6.155  1.00 14.96           C
ATOM    124  N   ASP A  16      25.873  60.887  -3.360  1.00 12.93           N
ATOM    125  CA  ASP A  16      27.292  60.642  -3.567  1.00 15.58           C
ATOM    126  C   ASP A  16      27.624  60.619  -5.051  1.00 16.44           C
ATOM    127  O   ASP A  16      26.792  60.259  -5.888  1.00 17.39           O
ATOM    128  CB  ASP A  16      27.718  59.325  -2.903  1.00 16.08           C
ATOM    129  CG  ASP A  16      27.580  59.399  -1.391  1.00 17.67           C
ATOM    130  OD1 ASP A  16      28.522  59.885  -0.715  1.00 21.90           O
ATOM    131  OD2 ASP A  16      26.529  59.046  -0.769  1.00 18.66           O
ATOM    132  N   GLN A  17      28.872  60.996  -5.330  1.00 21.30           N
ATOM    133  CA  GLN A  17      29.381  60.965  -6.692  1.00 25.06           C
ATOM    134  C   GLN A  17      29.886  59.565  -6.964  1.00 25.21           C
ATOM    135  O   GLN A  17      30.388  58.864  -6.078  1.00 26.76           O
ATOM    136  CB  GLN A  17      30.555  61.968  -6.858  1.00 27.80           C
ATOM    137  CG  GLN A  17      30.126  63.437  -6.697  1.00 34.95           C
ATOM    138  CD  GLN A  17      28.856  63.768  -7.461  1.00 40.64           C
ATOM    139  OE1 GLN A  17      28.890  63.948  -8.687  1.00 45.27           O
ATOM    140  NE2 GLN A  17      27.734  63.841  -6.754  1.00 44.64           N
ATOM    141  N   GLY A  18      29.808  59.167  -8.207  1.00 26.04           N
ATOM    142  CA  GLY A  18      30.404  57.892  -8.558  1.00 23.61           C
ATOM    143  C   GLY A  18      29.253  57.041  -9.058  1.00 22.95           C
ATOM    144  O   GLY A  18      28.079  57.389  -8.927  1.00 23.97           O
ATOM    145  N   ASP A  19      29.605  55.928  -9.696  1.00 19.46           N
ATOM    146  CA  ASP A  19      28.566  55.126 -10.303  1.00 15.13           C
ATOM    147  C   ASP A  19      28.675  53.767  -9.671  1.00 13.30           C
ATOM    148  O   ASP A  19      29.687  53.043  -9.834  1.00 14.96           O
ATOM    149  CB  ASP A  19      28.801  55.078 -11.815  1.00 15.80           C
ATOM    150  CG  ASP A  19      27.693  54.323 -12.543  1.00 14.82           C
ATOM    151  OD1 ASP A  19      27.397  54.694 -13.708  1.00 22.17           O
ATOM    152  OD2 ASP A  19      27.014  53.415 -12.012  1.00 13.19           O
ATOM    153  N   PRO A  20      27.676  53.345  -8.895  1.00 10.70           N
ATOM    154  CA  PRO A  20      27.815  52.111  -8.148  1.00 11.44           C
ATOM    155  C   PRO A  20      27.794  50.857  -9.034  1.00 11.73           C
ATOM    156  O   PRO A  20      28.133  49.785  -8.520  1.00 13.50           O
ATOM    157  CB  PRO A  20      26.577  52.089  -7.236  1.00 11.63           C
ATOM    158  CG  PRO A  20      25.536  52.923  -8.012  1.00 11.68           C
ATOM    159  CD  PRO A  20      26.354  53.992  -8.704  1.00 13.09           C
ATOM    160  N   ARG A  21      27.487  51.023 -10.307  1.00 10.30           N
ATOM    161  CA  ARG A  21      27.540  49.878 -11.218  1.00  9.94           C
ATOM    162  C   ARG A  21      28.981  49.463 -11.431  1.00 12.33           C
ATOM    163  O   ARG A  21      29.214  48.347 -11.894  1.00 11.88           O
ATOM    164  CB  ARG A  21      26.860  50.230 -12.541  1.00  9.53           C
ATOM    165  CG  ARG A  21      25.320  50.246 -12.351  1.00 12.08           C
ATOM    166  CD  ARG A  21      24.619  50.877 -13.551  1.00 13.29           C
ATOM    167  NE  ARG A  21      24.988  52.285 -13.741  1.00 11.04           N
ATOM    168  CZ  ARG A  21      24.332  53.100 -14.566  1.00 14.55           C
ATOM    169  NH1 ARG A  21      23.367  52.624 -15.329  1.00 15.02           N
ATOM    170  NH2 ARG A  21      24.646  54.393 -14.647  1.00 17.49           N
ATOM    171  N   LEU A  22      29.934  50.320 -11.100  1.00 12.18           N
ATOM    172  CA  LEU A  22      31.345  49.927 -11.105  1.00 14.51           C
ATOM    173  C   LEU A  22      31.857  49.483  -9.729  1.00 15.14           C
ATOM    174  O   LEU A  22      32.918  48.883  -9.632  1.00 17.84           O
ATOM    175  CB  LEU A  22      32.203  51.107 -11.619  1.00 14.34           C
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FIGURE 4C

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ATOM    176  CG  LEU A  22      32.122  51.159 -13.157  1.00 17.03           C
ATOM    177  CD1 LEU A  22      30.826  51.853 -13.602  1.00 19.85           C
ATOM    178  CD2 LEU A  22      33.357  51.826 -13.741  1.00 25.07           C
ATOM    179  N   LEU A  23      31.156  49.866  -8.653  1.00 13.13           N
ATOM    180  CA  LEU A  23      31.658  49.731  -7.300  1.00 11.50           C
ATOM    181  C   LEU A  23      31.136  48.525  -6.502  1.00 12.61           C
ATOM    182  O   LEU A  23      31.640  48.214  -5.426  1.00 15.30           O
ATOM    183  CB  LEU A  23      31.254  50.973  -6.494  1.00 11.09           C
ATOM    184  CG  LEU A  23      31.718  52.310  -7.093  1.00 14.53           C
ATOM    185  CD1 LEU A  23      31.083  53.439  -6.284  1.00 17.73           C
ATOM    186  CD2 LEU A  23      33.278  52.458  -7.056  1.00 19.49           C
ATOM    187  N   LEU A  24      30.117  47.860  -7.024  1.00 10.67           N
ATOM    188  CA  LEU A  24      29.472  46.769  -6.315  1.00  9.69           C
ATOM    189  C   LEU A  24      29.522  45.511  -7.175  1.00  9.07           C
ATOM    190  O   LEU A  24      29.640  45.575  -8.418  1.00 12.00           O
ATOM    191  CB  LEU A  24      27.982  47.126  -6.085  1.00 10.47           C
ATOM    192  CG  LEU A  24      27.719  48.442  -5.317  1.00 11.73           C
ATOM    193  CD1 LEU A  24      26.212  48.632  -5.202  1.00 12.94           C
ATOM    194  CD2 LEU A  24      28.362  48.259  -3.906  1.00 15.84           C
ATOM    195  N   ASP A  25      29.384  44.366  -6.533  1.00  9.18           N
ATOM    196  CA  ASP A  25      29.209  43.100  -7.268  1.00 11.54           C
ATOM    197  C   ASP A  25      28.442  42.104  -6.438  1.00 12.11           C
ATOM    198  O   ASP A  25      27.953  42.469  -5.350  1.00 12.78           O
ATOM    199  CB  ASP A  25      30.589  42.584  -7.726  1.00 12.54           C
ATOM    200  CG  ASP A  25      31.498  42.280  -6.571  1.00 19.17           C
ATOM    201  OD1 ASP A  25      32.601  42.851  -6.523  1.00 20.54           O
ATOM    202  OD2 ASP A  25      31.177  41.478  -5.657  1.00 22.03           O
ATOM    203  N   SER A  26      28.310  40.856  -6.927  1.00 12.85           N
ATOM    204  CA  SER A  26      27.654  39.786  -6.172  1.00 15.16           C
ATOM    205  C   SER A  26      26.224  40.125  -5.787  1.00 14.02           C
ATOM    206  O   SER A  26      25.815  39.942  -4.637  1.00 15.44           O
ATOM    207  CB  SER A  26      28.468  39.392  -4.906  1.00 15.47           C
ATOM    208  OG  SER A  26      29.796  39.109  -5.306  1.00 19.79           O
ATOM    209  N   TYR A  27      25.462  40.634  -6.733  1.00 12.48           N
ATOM    210  CA  TYR A  27      24.095  41.020  -6.456  1.00 11.57           C
ATOM    211  C   TYR A  27      23.207  39.841  -6.327  1.00 15.74           C
ATOM    212  O   TYR A  27      23.236  38.948  -7.181  1.00 15.92           O
ATOM    213  CB  TYR A  27      23.532  41.867  -7.616  1.00 12.55           C
ATOM    214  CG  TYR A  27      24.183  43.196  -7.881  1.00 12.17           C
ATOM    215  CD1 TYR A  27      23.648  44.383  -7.338  1.00 11.29           C
ATOM    216  CE1 TYR A  27      24.229  45.662  -7.606  1.00 13.77           C
ATOM    217  CZ  TYR A  27      25.389  45.709  -8.427  1.00 11.76           C
ATOM    218  OH  TYR A  27      25.907  46.910  -8.753  1.00 12.42           O
ATOM    219  CE2 TYR A  27      25.934  44.526  -8.979  1.00 10.35           C
ATOM    220  CD2 TYR A  27      25.329  43.295  -8.699  1.00 12.94           C
ATOM    221  N   VAL A  28      22.341  39.896  -5.322  1.00 14.82           N
ATOM    222  CA  VAL A  28      21.270  38.913  -5.169  1.00 17.64           C
ATOM    223  C   VAL A  28      19.981  39.626  -4.821  1.00 15.47           C
ATOM    224  O   VAL A  28      19.928  40.300  -3.818  1.00 16.40           O
ATOM    225  CB  VAL A  28      21.619  37.928  -4.030  1.00 17.98           C
ATOM    226  CG1 VAL A  28      20.422  36.952  -3.756  1.00 21.29           C
ATOM    227  CG2 VAL A  28      22.971  37.155  -4.301  1.00 21.24           C
ATOM    228  N   LYS A  29      18.918  39.479  -5.643  1.00 17.26           N
ATOM    229  CA  LYS A  29      17.623  40.098  -5.360  1.00 19.09           C
ATOM    230  C   LYS A  29      16.955  39.465  -4.150  1.00 21.14           C
ATOM    231  O   LYS A  29      16.820  38.221  -4.097  1.00 22.83           O
ATOM    232  CB  LYS A  29      16.705  40.042  -6.581  1.00 22.10           C
ATOM    233  CG  LYS A  29      15.420  40.856  -6.369  1.00 23.81           C
ATOM    234  CD  LYS A  29      14.628  40.912  -7.667  1.00 29.03           C
ATOM    235  CE  LYS A  29      13.166  40.797  -7.314  1.00 32.57           C
```

FIGURE 4D

ATOM	236	NZ	LYS	A	29	12.346	40.770	-8.562	1.00	35.07	N
ATOM	237	N	ILE	A	30	16.578	40.280	-3.182	1.00	20.16	N
ATOM	238	CA	ILE	A	30	15.970	39.734	-1.955	1.00	22.42	C
ATOM	239	C	ILE	A	30	14.610	40.324	-1.607	1.00	24.96	C
ATOM	240	O	ILE	A	30	13.981	39.883	-0.644	1.00	25.98	O
ATOM	241	CB	ILE	A	30	16.855	39.876	-0.720	1.00	21.78	C
ATOM	242	CG1	ILE	A	30	17.176	41.348	-0.421	1.00	21.08	C
ATOM	243	CD1	ILE	A	30	17.751	41.503	0.977	1.00	23.90	C
ATOM	244	CG2	ILE	A	30	18.109	39.003	-0.828	1.00	21.19	C
ATOM	245	N	GLY	A	31	14.180	41.328	-2.355	1.00	24.54	N
ATOM	246	CA	GLY	A	31	12.974	42.086	-2.027	1.00	27.36	C
ATOM	247	C	GLY	A	31	12.434	42.685	-3.315	1.00	27.39	C
ATOM	248	O	GLY	A	31	13.191	43.015	-4.234	1.00	24.68	O
ATOM	249	N	GLU	A	32	11.111	42.777	-3.412	1.00	29.35	N
ATOM	250	CA	GLU	A	32	10.500	43.477	-4.535	1.00	34.01	C
ATOM	251	C	GLU	A	32	9.260	44.239	-4.029	1.00	34.48	C
ATOM	252	O	GLU	A	32	8.537	43.811	-3.088	1.00	34.78	O
ATOM	253	CB	GLU	A	32	10.181	42.568	-5.741	1.00	35.60	C
ATOM	254	CG	GLU	A	32	10.174	43.334	-7.075	1.00	41.71	C
ATOM	255	CD	GLU	A	32	9.729	42.528	-8.305	1.00	46.73	C
ATOM	256	OE1	GLU	A	32	8.551	42.098	-8.370	1.00	50.73	O
ATOM	257	OE2	GLU	A	32	10.544	42.349	-9.249	1.00	48.84	O
ATOM	258	N	GLY	A	33	9.044	45.390	-4.641	1.00	32.68	N
ATOM	259	CA	GLY	A	33	8.041	46.324	-4.162	1.00	32.36	C
ATOM	260	C	GLY	A	33	7.418	46.911	-5.403	1.00	29.65	C
ATOM	261	O	GLY	A	33	7.779	46.538	-6.546	1.00	29.02	O
ATOM	262	N	SER	A	34	6.441	47.790	-5.196	1.00	29.93	N
ATOM	263	CA	SER	A	34	5.792	48.393	-6.351	1.00	28.24	C
ATOM	264	C	SER	A	34	6.677	49.426	-7.023	1.00	27.38	C
ATOM	265	O	SER	A	34	6.457	49.780	-8.167	1.00	27.56	O
ATOM	266	CB	SER	A	34	4.424	48.989	-5.984	1.00	27.18	C
ATOM	267	OG	SER	A	34	4.530	50.090	-5.086	1.00	29.14	O
ATOM	268	N	THR	A	35	7.687	49.906	-6.314	1.00	25.69	N
ATOM	269	CA	THR	A	35	8.459	51.023	-6.848	1.00	26.40	C
ATOM	270	C	THR	A	35	9.932	50.642	-7.060	1.00	26.80	C
ATOM	271	O	THR	A	35	10.738	51.492	-7.429	1.00	27.06	O
ATOM	272	CB	THR	A	35	8.350	52.302	-5.959	1.00	27.03	C
ATOM	273	OG1	THR	A	35	8.741	51.999	-4.601	1.00	32.51	O
ATOM	274	CG2	THR	A	35	6.926	52.800	-5.856	1.00	25.64	C
ATOM	275	N	GLY	A	36	10.279	49.377	-6.812	1.00	25.76	N
ATOM	276	CA	GLY	A	36	11.662	48.950	-7.013	1.00	24.96	C
ATOM	277	C	GLY	A	36	12.025	47.650	-6.347	1.00	26.10	C
ATOM	278	O	GLY	A	36	11.161	46.847	-5.980	1.00	24.93	O
ATOM	279	N	ILE	A	37	13.323	47.389	-6.248	1.00	21.07	N
ATOM	280	CA	ILE	A	37	13.763	46.137	-5.660	1.00	20.68	C
ATOM	281	C	ILE	A	37	14.810	46.385	-4.580	1.00	20.77	C
ATOM	282	O	ILE	A	37	15.290	47.514	-4.395	1.00	17.69	O
ATOM	283	CB	ILE	A	37	14.304	45.202	-6.733	1.00	21.29	C
ATOM	284	CG1	ILE	A	37	15.590	45.787	-7.358	1.00	21.98	C
ATOM	285	CD1	ILE	A	37	16.331	44.800	-8.270	1.00	24.25	C
ATOM	286	CG2	ILE	A	37	13.274	44.943	-7.852	1.00	24.04	C
ATOM	287	N	VAL	A	38	15.133	45.331	-3.822	1.00	16.94	N
ATOM	288	CA	VAL	A	38	16.261	45.380	-2.925	1.00	17.77	C
ATOM	289	C	VAL	A	38	17.176	44.236	-3.312	1.00	17.91	C
ATOM	290	O	VAL	A	38	16.701	43.121	-3.503	1.00	16.89	O
ATOM	291	CB	VAL	A	38	15.849	45.213	-1.464	1.00	20.06	C
ATOM	292	CG1	VAL	A	38	17.068	45.278	-0.574	1.00	19.53	C
ATOM	293	CG2	VAL	A	38	14.878	46.355	-1.058	1.00	22.63	C
ATOM	294	N	CYS	A	39	18.466	44.535	-3.504	1.00	15.90	N
ATOM	295	CA	CYS	A	39	19.462	43.492	-3.802	1.00	15.23	C

FIGURE 4E

```
ATOM    296  C    CYS A  39      20.487  43.558  -2.718  1.00 15.09           C
ATOM    297  O    CYS A  39      20.916  44.644  -2.307  1.00 18.31           O
ATOM    298  CB   CYS A  39      20.206  43.780  -5.085  1.00 17.71           C
ATOM    299  SG   CYS A  39      19.248  43.345  -6.531  1.00 29.98           S
ATOM    300  N    LEU A  40      20.935  42.404  -2.280  1.00 13.43           N
ATOM    301  CA   LEU A  40      22.176  42.366  -1.504  1.00 12.61           C
ATOM    302  C    LEU A  40      23.316  42.478  -2.461  1.00 13.56           C
ATOM    303  O    LEU A  40      23.229  41.998  -3.582  1.00 13.95           O
ATOM    304  CB BLEU A  40      22.205  41.014  -0.818  0.35 13.47           C
ATOM    305  CB ALEU A  40      22.313  41.061  -0.726  0.65 13.78           C
ATOM    306  CG BLEU A  40      23.084  40.728   0.369  0.35 13.46           C
ATOM    307  CG ALEU A  40      21.295  40.911   0.371  0.65 14.42           C
ATOM    308  CD1BLEU A  40      22.868  41.756   1.476  0.35 12.14           C
ATOM    309  CD1ALEU A  40      21.485  39.526   1.072  0.65 16.48           C
ATOM    310  CD2BLEU A  40      22.690  39.340   0.836  0.35 14.25           C
ATOM    311  CD2ALEU A  40      21.438  42.036   1.398  0.65 12.51           C
ATOM    312  N    ALA A  41      24.402  43.093  -2.059  1.00 11.04           N
ATOM    313  CA   ALA A  41      25.588  43.173  -2.932  1.00  9.78           C
ATOM    314  C    ALA A  41      26.776  43.339  -2.028  1.00 11.45           C
ATOM    315  O    ALA A  41      26.624  43.526  -0.806  1.00 12.40           O
ATOM    316  CB   ALA A  41      25.445  44.398  -3.909  1.00 11.45           C
ATOM    317  N    ARG A  42      27.957  43.287  -2.631  1.00 10.09           N
ATOM    318  CA   ARG A  42      29.214  43.485  -1.901  1.00 12.07           C
ATOM    319  C    ARG A  42      29.923  44.700  -2.438  1.00 12.90           C
ATOM    320  O    ARG A  42      29.991  44.899  -3.658  1.00 13.27           O
ATOM    321  CB   ARG A  42      30.129  42.285  -2.126  1.00 13.30           C
ATOM    322  CG   ARG A  42      29.677  40.964  -1.510  1.00 17.03           C
ATOM    323  CD   ARG A  42      30.194  40.836  -0.116  1.00 18.50           C
ATOM    324  NE   ARG A  42      29.707  39.625   0.515  1.00 20.90           N
ATOM    325  CZ   ARG A  42      30.001  39.313   1.774  1.00 21.98           C
ATOM    326  NH1  ARG A  42      30.809  40.101   2.484  1.00 20.65           N
ATOM    327  NH2  ARG A  42      29.485  38.235   2.323  1.00 24.90           N
ATOM    328  N    GLU A  43      30.447  45.538  -1.546  1.00 13.14           N
ATOM    329  CA   GLU A  43      31.287  46.651  -1.947  1.00 16.07           C
ATOM    330  C    GLU A  43      32.680  46.158  -2.283  1.00 17.93           C
ATOM    331  O    GLU A  43      33.280  45.318  -1.598  1.00 17.37           O
ATOM    332  CB   GLU A  43      31.356  47.712  -0.788  1.00 17.80           C
ATOM    333  CG   GLU A  43      30.062  48.500  -0.603  1.00 24.14           C
ATOM    334  CD   GLU A  43      30.170  49.753   0.323  1.00 36.79           C
ATOM    335  OE1  GLU A  43      29.840  50.931  -0.087  1.00 40.88           O
ATOM    336  OE2  GLU A  43      30.548  49.583   1.488  1.00 37.74           O
ATOM    337  N    LYS A  44      33.228  46.635  -3.401  1.00 18.53           N
ATOM    338  CA   LYS A  44      34.595  46.237  -3.710  1.00 20.85           C
ATOM    339  C    LYS A  44      35.580  46.850  -2.697  1.00 22.22           C
ATOM    340  O    LYS A  44      35.313  47.903  -2.153  1.00 24.01           O
ATOM    341  CB   LYS A  44      34.927  46.681  -5.150  1.00 20.91           C
ATOM    342  CG   LYS A  44      34.118  45.798  -6.134  1.00 21.24           C
ATOM    343  CD   LYS A  44      34.500  46.034  -7.588  1.00 23.03           C
ATOM    344  CE   LYS A  44      33.451  45.426  -8.513  1.00 21.79           C
ATOM    345  NZ   LYS A  44      33.802  43.999  -8.787  1.00 22.44           N
ATOM    346  N    HIS A  45      36.705  46.175  -2.448  1.00 24.80           N
ATOM    347  CA   HIS A  45      37.816  46.704  -1.561  1.00 28.55           C
ATOM    348  C    HIS A  45      37.590  46.436  -0.072  1.00 27.31           C
ATOM    349  O    HIS A  45      38.460  45.828   0.601  1.00 30.94           O
ATOM    350  CB   HIS A  45      38.113  48.222  -1.732  1.00 31.19           C
ATOM    351  CG   HIS A  45      38.483  48.624  -3.133  1.00 37.69           C
ATOM    352  ND1  HIS A  45      39.598  48.134  -3.782  1.00 42.26           N
ATOM    353  CE1  HIS A  45      39.656  48.649  -5.000  1.00 43.74           C
ATOM    354  NE2  HIS A  45      38.628  49.466  -5.160  1.00 41.58           N
ATOM    355  CD2  HIS A  45      37.885  49.477  -4.004  1.00 39.95           C
```

FIGURE 4F

```
ATOM    356  N   SER A  46      36.432  46.876   0.437  1.00 26.00           N
ATOM    357  CA  SER A  46      36.019  46.555   1.812  1.00 22.54           C
ATOM    358  C   SER A  46      35.367  45.198   1.963  1.00 20.76           C
ATOM    359  O   SER A  46      35.445  44.571   3.036  1.00 17.78           O
ATOM    360  CB  SER A  46      35.066  47.606   2.338  1.00 22.04           C
ATOM    361  OG  SER A  46      33.764  47.416   1.814  1.00 24.93           O
ATOM    362  N   GLY A  47      34.686  44.737   0.916  1.00 17.17           N
ATOM    363  CA  GLY A  47      34.033  43.468   1.021  1.00 16.12           C
ATOM    364  C   GLY A  47      32.692  43.563   1.705  1.00 15.11           C
ATOM    365  O   GLY A  47      32.043  42.570   1.848  1.00 16.73           O
ATOM    366  N   ARG A  48      32.308  44.755   2.122  1.00 15.32           N
ATOM    367  CA  ARG A  48      31.146  44.851   2.972  1.00 16.46           C
ATOM    368  C   ARG A  48      29.857  44.444   2.220  1.00 16.46           C
ATOM    369  O   ARG A  48      29.607  44.858   1.097  1.00 13.90           O
ATOM    370  CB  ARG A  48      31.066  46.292   3.466  1.00 18.28           C
ATOM    371  CG  ARG A  48      29.954  46.548   4.427  1.00 21.92           C
ATOM    372  CD  ARG A  48      30.146  47.877   5.198  1.00 24.00           C
ATOM    373  NE  ARG A  48      30.185  49.028   4.317  1.00 23.46           N
ATOM    374  CZ  ARG A  48      30.420  50.277   4.711  1.00 26.94           C
ATOM    375  NH1 ARG A  48      30.427  51.247   3.814  1.00 27.09           N
ATOM    376  NH2 ARG A  48      30.665  50.544   6.000  1.00 23.89           N
ATOM    377  N   GLN A  49      29.026  43.690   2.892  1.00 14.37           N
ATOM    378  CA  GLN A  49      27.714  43.347   2.371  1.00 16.62           C
ATOM    379  C   GLN A  49      26.784  44.519   2.622  1.00 15.48           C
ATOM    380  O   GLN A  49      26.757  45.084   3.735  1.00 17.38           O
ATOM    381  CB  GLN A  49      27.255  42.044   3.047  1.00 19.35           C
ATOM    382  CG  GLN A  49      25.973  41.508   2.537  1.00 25.61           C
ATOM    383  CD  GLN A  49      25.731  40.074   3.025  1.00 29.90           C
ATOM    384  OE1 GLN A  49      25.694  39.820   4.227  1.00 35.77           O
ATOM    385  NE2 GLN A  49      25.654  39.152   2.104  1.00 32.39           N
ATOM    386  N   VAL A  50      26.009  44.911   1.605  1.00 12.13           N
ATOM    387  CA  VAL A  50      25.077  46.052   1.738  1.00 12.23           C
ATOM    388  C   VAL A  50      23.753  45.665   1.139  1.00 12.53           C
ATOM    389  O   VAL A  50      23.675  44.827   0.240  1.00 13.60           O
ATOM    390  CB  VAL A  50      25.586  47.339   0.996  1.00 11.34           C
ATOM    391  CG1 VAL A  50      26.863  47.886   1.664  1.00 13.54           C
ATOM    392  CG2 VAL A  50      25.814  47.101  -0.481  1.00 11.75           C
ATOM    393  N   ALA A  51      22.683  46.261   1.655  1.00 11.02           N
ATOM    394  CA  ALA A  51      21.371  46.115   1.049  1.00 12.40           C
ATOM    395  C   ALA A  51      21.096  47.299   0.189  1.00 12.22           C
ATOM    396  O   ALA A  51      21.021  48.423   0.691  1.00 17.98           O
ATOM    397  CB  ALA A  51      20.298  46.028   2.152  1.00 14.02           C
ATOM    398  N   VAL A  52      20.943  47.067  -1.105  1.00 11.18           N
ATOM    399  CA  VAL A  52      20.844  48.199  -2.021  1.00 13.17           C
ATOM    400  C   VAL A  52      19.362  48.316  -2.351  1.00 13.63           C
ATOM    401  O   VAL A  52      18.811  47.448  -3.030  1.00 14.47           O
ATOM    402  CB  VAL A  52      21.629  47.962  -3.335  1.00 12.75           C
ATOM    403  CG1 VAL A  52      21.538  49.235  -4.289  1.00 11.81           C
ATOM    404  CG2 VAL A  52      23.068  47.576  -3.032  1.00 12.68           C
ATOM    405  N   LYS A  53      18.731  49.391  -1.895  1.00 14.05           N
ATOM    406  CA  LYS A  53      17.371  49.681  -2.341  1.00 15.39           C
ATOM    407  C   LYS A  53      17.473  50.432  -3.668  1.00 13.89           C
ATOM    408  O   LYS A  53      18.092  51.522  -3.724  1.00 14.24           O
ATOM    409  CB  LYS A  53      16.686  50.550  -1.319  1.00 17.12           C
ATOM    410  CG  LYS A  53      16.663  49.947   0.113  1.00 21.94           C
ATOM    411  CD  LYS A  53      16.074  50.989   1.134  1.00 26.70           C
ATOM    412  N   MET A  54      16.878  49.866  -4.712  1.00 13.18           N
ATOM    413  CA  MET A  54      16.929  50.430  -6.068  1.00 12.40           C
ATOM    414  C   MET A  54      15.532  50.906  -6.383  1.00 15.36           C
ATOM    415  O   MET A  54      14.665  50.073  -6.652  1.00 16.74           O
```

FIGURE 4G

```
ATOM    416  CB  MET A  54      17.342  49.389  -7.063  1.00 13.00           C
ATOM    417  CG  MET A  54      18.740  48.812  -6.710  1.00 13.28           C
ATOM    418  SD  MET A  54      19.114  47.326  -7.684  1.00 19.83           S
ATOM    419  CE  MET A  54      20.954  47.018  -7.327  1.00 15.36           C
ATOM    420  N   MET A  55      15.315  52.188  -6.258  1.00 15.00           N
ATOM    421  CA  MET A  55      13.969  52.799  -6.438  1.00 16.85           C
ATOM    422  C   MET A  55      13.754  53.445  -7.776  1.00 14.40           C
ATOM    423  O   MET A  55      14.524  54.299  -8.181  1.00 14.60           O
ATOM    424  CB BMET A  55      13.742  53.884  -5.371  0.35 15.51           C
ATOM    425  CB AMET A  55      13.667  53.823  -5.361  0.65 15.96           C
ATOM    426  CG BMET A  55      14.554  53.706  -4.098  0.35 18.74           C
ATOM    427  CG AMET A  55      13.248  53.182  -4.075  0.65 24.80           C
ATOM    428  SD BMET A  55      13.768  52.512  -3.033  0.35 21.92           S
ATOM    429  SD AMET A  55      13.737  54.316  -2.846  0.65 27.43           S
ATOM    430  CE BMET A  55      12.233  53.426  -2.562  0.35 21.78           C
ATOM    431  CE AMET A  55      15.399  53.802  -2.732  0.65 23.91           C
ATOM    432  N   ASP A  56      12.672  53.111  -8.457  1.00 15.55           N
ATOM    433  CA  ASP A  56      12.432  53.711  -9.753  1.00 15.83           C
ATOM    434  C   ASP A  56      11.720  55.035  -9.469  1.00 14.23           C
ATOM    435  O   ASP A  56      10.616  55.046  -8.944  1.00 16.20           O
ATOM    436  CB  ASP A  56      11.524  52.824 -10.603  1.00 18.00           C
ATOM    437  CG  ASP A  56      11.155  53.459 -11.954  1.00 23.66           C
ATOM    438  OD1 ASP A  56      11.356  54.676 -12.227  1.00 24.76           O
ATOM    439  OD2 ASP A  56      10.584  52.770 -12.826  1.00 31.97           O
ATOM    440  N   LEU A  57      12.387  56.141  -9.740  1.00 14.36           N
ATOM    441  CA  LEU A  57      11.876  57.452  -9.345  1.00 13.11           C
ATOM    442  C   LEU A  57      10.643  57.844 -10.122  1.00 16.49           C
ATOM    443  O   LEU A  57       9.887  58.714  -9.693  1.00 16.35           O
ATOM    444  CB  LEU A  57      12.968  58.556  -9.496  1.00 13.23           C
ATOM    445  CG  LEU A  57      14.131  58.333  -8.491  1.00 14.74           C
ATOM    446  CD1 LEU A  57      15.286  59.249  -8.835  1.00 16.01           C
ATOM    447  CD2 LEU A  57      13.619  58.607  -7.055  1.00 16.26           C
ATOM    448  N   ARG A  58      10.423  57.206 -11.258  1.00 16.47           N
ATOM    449  CA  ARG A  58       9.200  57.506 -12.031  1.00 20.66           C
ATOM    450  C   ARG A  58       7.983  56.927 -11.383  1.00 21.68           C
ATOM    451  O   ARG A  58       6.873  57.382 -11.637  1.00 27.31           O
ATOM    452  CB  ARG A  58       9.342  56.984 -13.456  1.00 22.28           C
ATOM    453  CG  ARG A  58      10.282  57.837 -14.281  1.00 25.01           C
ATOM    454  CD  ARG A  58      10.810  57.178 -15.512  1.00 30.40           C
ATOM    455  NE  ARG A  58      11.205  55.808 -15.233  1.00 33.95           N
ATOM    456  CZ  ARG A  58      11.740  54.977 -16.114  1.00 39.54           C
ATOM    457  NH1 ARG A  58      11.993  55.372 -17.365  1.00 42.52           N
ATOM    458  NH2 ARG A  58      12.042  53.744 -15.732  1.00 41.70           N
ATOM    459  N   LYS A  59       8.170  55.919 -10.538  1.00 19.43           N
ATOM    460  CA  LYS A  59       7.068  55.283  -9.841  1.00 20.52           C
ATOM    461  C   LYS A  59       6.932  55.781  -8.404  1.00 21.10           C
ATOM    462  O   LYS A  59       5.851  55.747  -7.810  1.00 21.07           O
ATOM    463  CB  LYS A  59       7.252  53.764  -9.867  1.00 20.25           C
ATOM    464  CG  LYS A  59       7.221  53.194 -11.289  1.00 24.36           C
ATOM    465  CD  LYS A  59       7.284  51.686 -11.236  1.00 28.81           C
ATOM    466  CE  LYS A  59       7.118  51.103 -12.636  1.00 36.29           C
ATOM    467  NZ  LYS A  59       7.341  49.618 -12.595  1.00 41.43           N
ATOM    468  N   GLN A  60       8.062  56.183  -7.819  1.00 20.52           N
ATOM    469  CA  GLN A  60       8.085  56.580  -6.416  1.00 20.62           C
ATOM    470  C   GLN A  60       7.205  57.777  -6.168  1.00 19.66           C
ATOM    471  O   GLN A  60       7.186  58.767  -6.948  1.00 19.92           O
ATOM    472  CB  GLN A  60       9.528  56.943  -6.031  1.00 20.76           C
ATOM    473  CG  GLN A  60       9.658  57.320  -4.544  1.00 24.20           C
ATOM    474  CD  GLN A  60       9.442  56.154  -3.617  1.00 25.06           C
ATOM    475  OE1 GLN A  60       9.058  56.349  -2.451  1.00 31.15           O
```

FIGURE 4H

```
ATOM    476  NE2 GLN A  60       9.683  54.936  -4.098  1.00 26.98           N
ATOM    477  N   GLN A  61       6.443  57.717  -5.061  1.00 18.63           N
ATOM    478  CA  GLN A  61       5.646  58.853  -4.656  1.00 19.20           C
ATOM    479  C   GLN A  61       6.238  59.323  -3.329  1.00 16.91           C
ATOM    480  O   GLN A  61       7.096  58.618  -2.792  1.00 17.73           O
ATOM    481  CB  GLN A  61       4.152  58.480  -4.562  1.00 18.77           C
ATOM    482  CG  GLN A  61       3.566  58.142  -5.969  1.00 26.87           C
ATOM    483  CD  GLN A  61       2.129  57.645  -5.913  1.00 33.51           C
ATOM    484  OE1 GLN A  61       1.336  58.080  -5.039  1.00 40.50           O
ATOM    485  NE2 GLN A  61       1.776  56.722  -6.814  1.00 34.57           N
ATOM    486  N   ARG A  62       5.820  60.506  -2.864  1.00 16.49           N
ATOM    487  CA  ARG A  62       6.428  61.168  -1.704  1.00 15.26           C
ATOM    488  C   ARG A  62       7.912  61.226  -1.901  1.00 15.96           C
ATOM    489  O   ARG A  62       8.688  60.840  -1.002  1.00 14.67           O
ATOM    490  CB  ARG A  62       6.064  60.472  -0.370  1.00 15.13           C
ATOM    491  CG  ARG A  62       4.554  60.425  -0.167  1.00 16.67           C
ATOM    492  CD  ARG A  62       4.222  60.474   1.316  1.00 17.55           C
ATOM    493  NE  ARG A  62       4.433  59.142   1.922  1.00 17.21           N
ATOM    494  CZ  ARG A  62       3.878  58.794   3.096  1.00 17.75           C
ATOM    495  NH1 ARG A  62       4.068  57.592   3.620  1.00 17.79           N
ATOM    496  NH2 ARG A  62       3.124  59.698   3.704  1.00 16.47           N
ATOM    497  N   ARG A  63       8.346  61.685  -3.087  1.00 15.72           N
ATOM    498  CA  ARG A  63       9.807  61.665  -3.355  1.00 13.77           C
ATOM    499  C   ARG A  63      10.519  62.623  -2.416  1.00 14.07           C
ATOM    500  O   ARG A  63      11.696  62.465  -2.163  1.00 13.33           O
ATOM    501  CB  ARG A  63      10.075  62.072  -4.821  1.00 15.62           C
ATOM    502  CG  ARG A  63       9.560  61.016  -5.747  1.00 13.62           C
ATOM    503  CD  ARG A  63       9.451  61.482  -7.239  1.00 18.07           C
ATOM    504  NE  ARG A  63       8.407  62.486  -7.226  1.00 19.25           N
ATOM    505  CZ  ARG A  63       8.334  63.575  -7.995  1.00 23.67           C
ATOM    506  NH1 ARG A  63       7.335  64.461  -7.798  1.00 25.09           N
ATOM    507  NH2 ARG A  63       9.202  63.747  -8.988  1.00 18.57           N
ATOM    508  N   GLU A  64       9.803  63.616  -1.909  1.00 14.50           N
ATOM    509  CA  GLU A  64      10.407  64.556  -0.973  1.00 17.59           C
ATOM    510  C   GLU A  64      11.009  63.830   0.228  1.00 15.22           C
ATOM    511  O   GLU A  64      12.055  64.284   0.704  1.00 14.88           O
ATOM    512  CB  GLU A  64       9.463  65.638  -0.466  1.00 19.82           C
ATOM    513  CG  GLU A  64       8.210  65.187   0.284  1.00 28.36           C
ATOM    514  CD  GLU A  64       7.064  64.624  -0.576  1.00 36.29           C
ATOM    515  OE1 GLU A  64       7.100  64.665  -1.867  1.00 33.16           O
ATOM    516  OE2 GLU A  64       6.096  64.115   0.084  1.00 39.40           O
ATOM    517  N   LEU A  65      10.368  62.754   0.663  1.00 13.41           N
ATOM    518  CA  LEU A  65      10.893  61.978   1.818  1.00 12.09           C
ATOM    519  C   LEU A  65      12.220  61.313   1.520  1.00 13.33           C
ATOM    520  O   LEU A  65      13.056  61.191   2.418  1.00 13.38           O
ATOM    521  CB  LEU A  65       9.898  60.922   2.339  1.00 12.36           C
ATOM    522  CG  LEU A  65       8.557  61.517   2.624  1.00 11.55           C
ATOM    523  CD1 LEU A  65       7.686  60.399   3.203  1.00 15.36           C
ATOM    524  CD2 LEU A  65       8.659  62.704   3.592  1.00 14.28           C
ATOM    525  N   LEU A  66      12.408  60.811   0.283  1.00 13.19           N
ATOM    526  CA  LEU A  66      13.703  60.208  -0.093  1.00 13.88           C
ATOM    527  C   LEU A  66      14.756  61.292  -0.066  1.00 15.69           C
ATOM    528  O   LEU A  66      15.863  61.101   0.434  1.00 14.61           O
ATOM    529  CB  LEU A  66      13.659  59.636  -1.530  1.00 16.89           C
ATOM    530  CG  LEU A  66      12.676  58.532  -1.843  1.00 21.31           C
ATOM    531  CD1 LEU A  66      12.768  58.297  -3.354  1.00 24.66           C
ATOM    532  CD2 LEU A  66      13.045  57.279  -1.076  1.00 24.73           C
ATOM    533  N   PHE A  67      14.425  62.448  -0.646  1.00 13.46           N
ATOM    534  CA  PHE A  67      15.345  63.567  -0.626  1.00 13.17           C
ATOM    535  C   PHE A  67      15.754  63.942   0.811  1.00 11.21           C
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FIGURE 4I

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ATOM    536  O   PHE A  67      16.916  64.092   1.130  1.00 12.87           O
ATOM    537  CB  PHE A  67      14.685  64.774  -1.349  1.00 12.78           C
ATOM    538  CG  PHE A  67      15.596  65.943  -1.500  1.00 15.41           C
ATOM    539  CD1 PHE A  67      16.503  66.021  -2.595  1.00 18.19           C
ATOM    540  CE1 PHE A  67      17.344  67.132  -2.722  1.00 18.52           C
ATOM    541  CZ  PHE A  67      17.333  68.149  -1.763  1.00 20.79           C
ATOM    542  CE2 PHE A  67      16.456  68.062  -0.680  1.00 20.02           C
ATOM    543  CD2 PHE A  67      15.592  66.955  -0.568  1.00 17.30           C
ATOM    544  N   ASN A  68      14.748  64.105   1.678  1.00 12.96           N
ATOM    545  CA  ASN A  68      15.077  64.562   3.015  1.00 12.14           C
ATOM    546  C   ASN A  68      15.965  63.544   3.732  1.00 11.06           C
ATOM    547  O   ASN A  68      16.878  63.964   4.433  1.00 12.48           O
ATOM    548  CB  ASN A  68      13.815  64.722   3.866  1.00 13.20           C
ATOM    549  CG  ASN A  68      12.915  65.783   3.357  1.00 13.46           C
ATOM    550  OD1 ASN A  68      13.354  66.704   2.648  1.00 16.36           O
ATOM    551  ND2 ASN A  68      11.624  65.684   3.711  1.00 15.19           N
ATOM    552  N   GLU A  69      15.629  62.261   3.625  1.00 10.11           N
ATOM    553  CA  GLU A  69      16.454  61.221   4.278  1.00 12.28           C
ATOM    554  C   GLU A  69      17.892  61.208   3.767  1.00 12.73           C
ATOM    555  O   GLU A  69      18.809  61.075   4.538  1.00 13.29           O
ATOM    556  CB  GLU A  69      15.839  59.813   4.105  1.00 12.61           C
ATOM    557  CG  GLU A  69      16.573  58.779   4.932  1.00 16.50           C
ATOM    558  CD  GLU A  69      15.914  57.453   4.867  1.00 23.66           C
ATOM    559  OE1 GLU A  69      14.754  57.368   4.366  1.00 23.07           O
ATOM    560  OE2 GLU A  69      16.552  56.491   5.339  1.00 23.27           O
ATOM    561  N   VAL A  70      18.081  61.366   2.466  1.00 12.91           N
ATOM    562  CA  VAL A  70      19.456  61.405   1.953  1.00 13.94           C
ATOM    563  C   VAL A  70      20.187  62.627   2.457  1.00 15.67           C
ATOM    564  O   VAL A  70      21.347  62.527   2.910  1.00 18.39           O
ATOM    565  CB  VAL A  70      19.491  61.365   0.403  1.00 15.95           C
ATOM    566  CG1 VAL A  70      20.933  61.689  -0.086  1.00 19.15           C
ATOM    567  CG2 VAL A  70      18.993  59.979  -0.088  1.00 16.29           C
ATOM    568  N   VAL A  71      19.549  63.800   2.408  1.00 13.10           N
ATOM    569  CA  VAL A  71      20.216  65.022   2.835  1.00 15.04           C
ATOM    570  C   VAL A  71      20.531  65.000   4.331  1.00 15.18           C
ATOM    571  O   VAL A  71      21.597  65.419   4.766  1.00 16.38           O
ATOM    572  CB  VAL A  71      19.327  66.231   2.539  1.00 16.36           C
ATOM    573  CG1 VAL A  71      19.916  67.516   3.145  1.00 23.11           C
ATOM    574  CG2 VAL A  71      19.235  66.392   1.066  1.00 20.39           C
ATOM    575  N   ILE A  72      19.587  64.504   5.125  1.00 14.45           N
ATOM    576  CA  ILE A  72      19.762  64.605   6.572  1.00 14.74           C
ATOM    577  C   ILE A  72      20.658  63.509   7.069  1.00 15.25           C
ATOM    578  O   ILE A  72      21.602  63.806   7.816  1.00 18.20           O
ATOM    579  CB  ILE A  72      18.387  64.547   7.300  1.00 13.58           C
ATOM    580  CG1 ILE A  72      17.574  65.759   6.893  1.00 12.87           C
ATOM    581  CD1 ILE A  72      16.090  65.761   7.362  1.00 13.66           C
ATOM    582  CG2 ILE A  72      18.596  64.471   8.836  1.00 14.60           C
ATOM    583  N   MET A  73      20.398  62.254   6.694  1.00 13.90           N
ATOM    584  CA  MET A  73      21.054  61.133   7.376  1.00 15.98           C
ATOM    585  C   MET A  73      22.432  60.754   6.831  1.00 17.84           C
ATOM    586  O   MET A  73      23.171  59.978   7.441  1.00 17.77           O
ATOM    587  CB  MET A  73      20.133  59.914   7.453  1.00 15.79           C
ATOM    588  CG  MET A  73      18.934  60.190   8.379  1.00 15.32           C
ATOM    589  SD  MET A  73      19.392  60.663  10.070  1.00 16.30           S
ATOM    590  CE  MET A  73      20.181  59.111  10.621  1.00 17.22           C
ATOM    591  N   ARG A  74      22.794  61.345   5.701  1.00 18.37           N
ATOM    592  CA  ARG A  74      24.024  60.912   5.081  1.00 22.44           C
ATOM    593  C   ARG A  74      25.217  61.169   5.994  1.00 24.52           C
ATOM    594  O   ARG A  74      26.097  60.311   6.104  1.00 27.75           O
ATOM    595  CB  ARG A  74      24.206  61.518   3.686  1.00 23.00           C
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FIGURE 4J

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ATOM    596  CG  ARG A  74      25.480  60.985   2.929  1.00 22.74           C
ATOM    597  CD  ARG A  74      25.589  59.430   2.618  1.00 22.85           C
ATOM    598  NE  ARG A  74      26.926  59.224   2.000  1.00 25.04           N
ATOM    599  CZ  ARG A  74      28.078  59.243   2.692  1.00 26.56           C
ATOM    600  NH1 ARG A  74      29.239  59.085   2.044  1.00 25.26           N
ATOM    601  NH2 ARG A  74      28.072  59.386   4.045  1.00 24.17           N
ATOM    602  N   ASP A  75      25.230  62.299   6.685  1.00 24.42           N
ATOM    603  CA  ASP A  75      26.407  62.661   7.440  1.00 25.42           C
ATOM    604  C   ASP A  75      26.306  62.355   8.979  1.00 25.26           C
ATOM    605  O   ASP A  75      27.145  62.798   9.739  1.00 25.72           O
ATOM    606  CB BASP A  75      26.760  64.135   7.190  0.35 26.70           C
ATOM    607  CB AASP A  75      26.779  64.131   7.167  0.65 27.91           C
ATOM    608  N   TYR A  76      25.314  61.558   9.404  1.00 18.52           N
ATOM    609  CA  TYR A  76      25.238  61.063  10.801  1.00 17.52           C
ATOM    610  C   TYR A  76      25.571  59.569  10.854  1.00 17.12           C
ATOM    611  O   TYR A  76      25.435  58.843   9.859  1.00 19.50           O
ATOM    612  CB  TYR A  76      23.844  61.320  11.399  1.00 16.15           C
ATOM    613  CG  TYR A  76      23.529  62.809  11.478  1.00 14.46           C
ATOM    614  CD1 TYR A  76      24.370  63.681  12.192  1.00 17.70           C
ATOM    615  CE1 TYR A  76      24.118  65.077  12.233  1.00 19.31           C
ATOM    616  CZ  TYR A  76      23.011  65.608  11.567  1.00 18.49           C
ATOM    617  OH  TYR A  76      22.755  66.931  11.664  1.00 23.24           O
ATOM    618  CE2 TYR A  76      22.172  64.758  10.864  1.00 15.69           C
ATOM    619  CD2 TYR A  76      22.438  63.361  10.810  1.00 16.31           C
ATOM    620  N   GLN A  77      26.035  59.102  11.992  1.00 14.90           N
ATOM    621  CA  GLN A  77      26.266  57.664  12.136  1.00 15.54           C
ATOM    622  C   GLN A  77      26.204  57.374  13.611  1.00 14.41           C
ATOM    623  O   GLN A  77      26.785  58.118  14.406  1.00 15.81           O
ATOM    624  CB  GLN A  77      27.699  57.270  11.657  1.00 18.19           C
ATOM    625  CG  GLN A  77      28.072  55.734  11.772  1.00 23.37           C
ATOM    626  CD  GLN A  77      28.614  55.207  13.186  1.00 26.91           C
ATOM    627  OE1 GLN A  77      28.420  54.018  13.544  1.00 29.00           O
ATOM    628  NE2 GLN A  77      29.283  56.066  13.939  1.00 29.67           N
ATOM    629  N   HIS A  78      25.621  56.237  13.936  1.00 12.38           N
ATOM    630  CA  HIS A  78      25.579  55.764  15.317  1.00  9.38           C
ATOM    631  C   HIS A  78      25.341  54.265  15.321  1.00 10.65           C
ATOM    632  O   HIS A  78      24.614  53.741  14.473  1.00 12.69           O
ATOM    633  CB  HIS A  78      24.476  56.478  16.090  1.00 10.58           C
ATOM    634  CG  HIS A  78      24.413  56.104  17.540  1.00 10.93           C
ATOM    635  ND1 HIS A  78      24.958  56.900  18.537  1.00 17.77           N
ATOM    636  CE1 HIS A  78      24.770  56.316  19.705  1.00 12.73           C
ATOM    637  NE2 HIS A  78      24.127  55.176  19.501  1.00 16.66           N
ATOM    638  CD2 HIS A  78      23.880  55.024  18.154  1.00  9.48           C
ATOM    639  N   PHE A  79      25.943  53.570  16.298  1.00 12.85           N
ATOM    640  CA  PHE A  79      25.831  52.108  16.289  1.00 13.99           C
ATOM    641  C   PHE A  79      24.422  51.594  16.426  1.00 12.74           C
ATOM    642  O   PHE A  79      24.151  50.454  16.056  1.00 15.25           O
ATOM    643  CB  PHE A  79      26.697  51.436  17.375  1.00 15.70           C
ATOM    644  CG  PHE A  79      27.094  50.017  17.026  1.00 23.71           C
ATOM    645  N   ASN A  80      23.535  52.407  17.015  1.00 11.50           N
ATOM    646  CA  ASN A  80      22.168  51.992  17.211  1.00 11.01           C
ATOM    647  C   ASN A  80      21.243  52.579  16.160  1.00 10.32           C
ATOM    648  O   ASN A  80      20.039  52.607  16.335  1.00 10.59           O
ATOM    649  CB  ASN A  80      21.642  52.378  18.606  1.00 12.14           C
ATOM    650  CG  ASN A  80      22.321  51.578  19.718  1.00 15.81           C
ATOM    651  OD1 ASN A  80      22.970  52.157  20.569  1.00 23.90           O
ATOM    652  ND2 ASN A  80      22.159  50.267  19.710  1.00 19.55           N
ATOM    653  N   VAL A  81      21.814  53.065  15.039  1.00  9.07           N
ATOM    654  CA  VAL A  81      20.987  53.539  13.887  1.00  8.92           C
ATOM    655  C   VAL A  81      21.419  52.771  12.654  1.00  7.73           C
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FIGURE 4K

```
ATOM    656  O   VAL A  81      22.630  52.675  12.359  1.00  8.95           O
ATOM    657  CB  VAL A  81      21.225  55.033  13.691  1.00  8.16           C
ATOM    658  CG1 VAL A  81      20.581  55.533  12.401  1.00 10.66           C
ATOM    659  CG2 VAL A  81      20.765  55.865  14.944  1.00  9.57           C
ATOM    660  N   VAL A  82      20.446  52.191  11.966  1.00  8.42           N
ATOM    661  CA  VAL A  82      20.763  51.445  10.730  1.00  7.72           C
ATOM    662  C   VAL A  82      21.379  52.442   9.747  1.00  8.94           C
ATOM    663  O   VAL A  82      20.759  53.483   9.413  1.00 10.35           O
ATOM    664  CB  VAL A  82      19.494  50.833  10.165  1.00 10.01           C
ATOM    665  CG1 VAL A  82      19.824  50.119   8.839  1.00 12.08           C
ATOM    666  CG2 VAL A  82      18.927  49.832  11.162  1.00 12.64           C
ATOM    667  N   GLU A  83      22.610  52.140   9.308  1.00 10.70           N
ATOM    668  CA  GLU A  83      23.375  53.129   8.600  1.00 11.89           C
ATOM    669  C   GLU A  83      23.089  53.185   7.122  1.00 12.81           C
ATOM    670  O   GLU A  83      22.988  52.158   6.454  1.00 14.07           O
ATOM    671  CB  GLU A  83      24.897  52.834   8.796  1.00 12.73           C
ATOM    672  CG  GLU A  83      25.818  53.960   8.295  1.00 16.96           C
ATOM    673  CD  GLU A  83      27.313  53.730   8.594  1.00 19.90           C
ATOM    674  OE1 GLU A  83      27.704  52.860   9.444  1.00 21.39           O
ATOM    675  OE2 GLU A  83      28.103  54.487   7.949  1.00 25.16           O
ATOM    676  N   MET A  84      22.941  54.406   6.633  1.00 12.37           N
ATOM    677  CA  MET A  84      22.903  54.658   5.196  1.00 13.43           C
ATOM    678  C   MET A  84      24.289  54.957   4.729  1.00 15.27           C
ATOM    679  O   MET A  84      24.853  56.035   5.049  1.00 15.52           O
ATOM    680  CB  MET A  84      21.982  55.843   4.869  1.00 16.45           C
ATOM    681  CG  MET A  84      21.993  56.101   3.361  1.00 19.85           C
ATOM    682  SD  MET A  84      21.214  57.739   2.997  1.00 30.09           S
ATOM    683  CE  MET A  84      19.620  57.360   3.393  1.00 27.67           C
ATOM    684  N   TYR A  85      24.875  54.025   3.978  1.00 10.98           N
ATOM    685  CA  TYR A  85      26.293  54.219   3.628  1.00 10.62           C
ATOM    686  C   TYR A  85      26.504  55.208   2.511  1.00 12.33           C
ATOM    687  O   TYR A  85      27.449  55.991   2.564  1.00 14.14           O
ATOM    688  CB  TYR A  85      26.894  52.905   3.175  1.00  8.90           C
ATOM    689  CG  TYR A  85      26.868  51.818   4.228  1.00 10.43           C
ATOM    690  CD1 TYR A  85      26.306  50.570   3.911  1.00 13.38           C
ATOM    691  CE1 TYR A  85      26.325  49.523   4.819  1.00 14.61           C
ATOM    692  CZ  TYR A  85      26.863  49.741   6.079  1.00 13.44           C
ATOM    693  OH  TYR A  85      26.861  48.672   6.980  1.00 17.07           O
ATOM    694  CE2 TYR A  85      27.391  50.975   6.449  1.00 13.82           C
ATOM    695  CD2 TYR A  85      27.397  52.033   5.477  1.00 12.40           C
ATOM    696  N   LYS A  86      25.666  55.116   1.495  1.00 10.58           N
ATOM    697  CA  LYS A  86      25.810  55.951   0.281  1.00 12.00           C
ATOM    698  C   LYS A  86      24.438  56.056  -0.396  1.00 10.65           C
ATOM    699  O   LYS A  86      23.543  55.199  -0.201  1.00 12.23           O
ATOM    700  CB  LYS A  86      26.718  55.275  -0.739  1.00 13.28           C
ATOM    701  CG  LYS A  86      28.193  55.033  -0.332  1.00 17.08           C
ATOM    702  CD BLYS A  86      29.052  56.234  -0.597  0.35 17.52           C
ATOM    703  CD ALYS A  86      28.985  56.308  -0.300  0.65 21.07           C
ATOM    704  CE BLYS A  86      30.513  55.885  -0.312  0.35 18.61           C
ATOM    705  CE ALYS A  86      30.434  55.995   0.074  0.65 24.99           C
ATOM    706  NZ BLYS A  86      30.746  55.897   1.159  0.35 17.16           N
ATOM    707  NZ ALYS A  86      31.288  57.208  -0.072  0.65 28.26           N
ATOM    708  N   SER A  87      24.256  57.088  -1.209  1.00 10.03           N
ATOM    709  CA  SER A  87      23.131  57.131  -2.122  1.00 11.42           C
ATOM    710  C   SER A  87      23.681  57.575  -3.460  1.00 11.39           C
ATOM    711  O   SER A  87      24.658  58.325  -3.518  1.00 11.68           O
ATOM    712  CB  SER A  87      22.016  58.120  -1.685  1.00 12.94           C
ATOM    713  OG  SER A  87      22.489  59.463  -1.724  1.00 20.40           O
ATOM    714  N   TYR A  88      23.079  57.035  -4.524  1.00 10.06           N
ATOM    715  CA  TYR A  88      23.496  57.356  -5.879  1.00  9.14           C
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FIGURE 4L

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ATOM    716  C   TYR A  88      22.332  57.511  -6.793  1.00 10.75           C
ATOM    717  O   TYR A  88      21.370  56.778  -6.676  1.00 10.73           O
ATOM    718  CB  TYR A  88      24.364  56.167  -6.444  1.00 10.44           C
ATOM    719  CG  TYR A  88      25.617  55.878  -5.680  1.00  9.26           C
ATOM    720  CD1 TYR A  88      25.690  54.784  -4.828  1.00 10.69           C
ATOM    721  CE1 TYR A  88      26.854  54.440  -4.195  1.00 13.14           C
ATOM    722  CZ  TYR A  88      27.986  55.180  -4.392  1.00 11.93           C
ATOM    723  OH  TYR A  88      29.125  54.804  -3.710  1.00 14.94           O
ATOM    724  CE2 TYR A  88      27.976  56.285  -5.215  1.00 12.64           C
ATOM    725  CD2 TYR A  88      26.777  56.608  -5.916  1.00 10.34           C
ATOM    726  N   LEU A  89      22.448  58.437  -7.758  1.00 10.01           N
ATOM    727  CA  LEU A  89      21.486  58.554  -8.803  1.00 11.44           C
ATOM    728  C   LEU A  89      22.037  57.764  -9.988  1.00 13.02           C
ATOM    729  O   LEU A  89      23.113  58.060 -10.506  1.00 15.98           O
ATOM    730  CB  LEU A  89      21.239  60.032  -9.168  1.00 12.87           C
ATOM    731  CG  LEU A  89      20.269  60.243 -10.313  1.00 17.18           C
ATOM    732  CD1 LEU A  89      18.849  59.775  -9.933  1.00 16.35           C
ATOM    733  CD2 LEU A  89      20.225  61.742 -10.559  1.00 20.37           C
ATOM    734  N   VAL A  90      21.315  56.725 -10.360  1.00 11.48           N
ATOM    735  CA  VAL A  90      21.732  55.741 -11.363  1.00 12.41           C
ATOM    736  C   VAL A  90      20.692  55.685 -12.473  1.00 15.35           C
ATOM    737  O   VAL A  90      19.701  54.981 -12.367  1.00 15.17           O
ATOM    738  CB  VAL A  90      21.863  54.346 -10.719  1.00 13.19           C
ATOM    739  CG1 VAL A  90      22.591  53.392 -11.649  1.00 16.49           C
ATOM    740  CG2 VAL A  90      22.632  54.394  -9.378  1.00 13.77           C
ATOM    741  N   GLY A  91      20.908  56.500 -13.502  1.00 18.11           N
ATOM    742  CA  GLY A  91      19.893  56.635 -14.549  1.00 19.22           C
ATOM    743  C   GLY A  91      18.595  57.208 -13.992  1.00 18.10           C
ATOM    744  O   GLY A  91      18.603  58.330 -13.459  1.00 19.82           O
ATOM    745  N   GLU A  92      17.519  56.431 -14.032  1.00 18.47           N
ATOM    746  CA  GLU A  92      16.245  56.914 -13.492  1.00 19.58           C
ATOM    747  C   GLU A  92      15.989  56.412 -12.083  1.00 19.05           C
ATOM    748  O   GLU A  92      14.852  56.553 -11.585  1.00 17.35           O
ATOM    749  CB  GLU A  92      15.067  56.434 -14.350  1.00 21.87           C
ATOM    750  CG  GLU A  92      15.391  56.457 -15.827  1.00 25.46           C
ATOM    751  CD  GLU A  92      15.592  57.871 -16.320  1.00 31.82           C
ATOM    752  OE1 GLU A  92      14.979  58.815 -15.763  1.00 32.34           O
ATOM    753  OE2 GLU A  92      16.381  58.046 -17.279  1.00 37.57           O
ATOM    754  N   GLU A  93      16.982  55.763 -11.473  1.00 14.94           N
ATOM    755  CA  GLU A  93      16.797  55.123 -10.199  1.00 14.61           C
ATOM    756  C   GLU A  93      17.614  55.812  -9.145  1.00 13.21           C
ATOM    757  O   GLU A  93      18.680  56.344  -9.429  1.00 13.71           O
ATOM    758  CB  GLU A  93      17.226  53.656 -10.252  1.00 16.06           C
ATOM    759  CG  GLU A  93      16.186  52.848 -11.050  1.00 18.66           C
ATOM    760  CD  GLU A  93      16.510  51.368 -11.146  1.00 29.04           C
ATOM    761  OE1 GLU A  93      17.633  50.963 -10.828  1.00 27.54           O
ATOM    762  OE2 GLU A  93      15.605  50.587 -11.546  1.00 34.55           O
ATOM    763  N   LEU A  94      17.121  55.784  -7.917  1.00 12.92           N
ATOM    764  CA  LEU A  94      17.956  56.176  -6.790  1.00 11.80           C
ATOM    765  C   LEU A  94      18.373  54.851  -6.147  1.00 10.79           C
ATOM    766  O   LEU A  94      17.510  54.014  -5.822  1.00 11.95           O
ATOM    767  CB  LEU A  94      17.138  57.024  -5.825  1.00 10.58           C
ATOM    768  CG  LEU A  94      17.877  57.424  -4.537  1.00 14.05           C
ATOM    769  CD1 LEU A  94      18.971  58.478  -4.809  1.00 16.12           C
ATOM    770  CD2 LEU A  94      16.851  57.946  -3.488  1.00 16.00           C
ATOM    771  N   TRP A  95      19.669  54.636  -5.966  1.00  9.59           N
ATOM    772  CA  TRP A  95      20.156  53.478  -5.211  1.00  9.80           C
ATOM    773  C   TRP A  95      20.642  53.937  -3.865  1.00 11.66           C
ATOM    774  O   TRP A  95      21.510  54.804  -3.772  1.00 11.31           O
ATOM    775  CB  TRP A  95      21.352  52.841  -5.946  1.00  8.99           C
```

FIGURE 4M

ATOM	776	CG	TRP	A	95	21.005	52.139	-7.199	1.00	9.92	C
ATOM	777	CD1	TRP	A	95	19.837	52.210	-7.928	1.00	11.08	C
ATOM	778	NE1	TRP	A	95	19.919	51.360	-9.021	1.00	13.91	N
ATOM	779	CE2	TRP	A	95	21.118	50.694	-8.983	1.00	10.77	C
ATOM	780	CD2	TRP	A	95	21.808	51.118	-7.818	1.00	10.93	C
ATOM	781	CE3	TRP	A	95	23.091	50.589	-7.541	1.00	10.76	C
ATOM	782	CZ3	TRP	A	95	23.637	49.618	-8.424	1.00	12.84	C
ATOM	783	CH2	TRP	A	95	22.936	49.217	-9.579	1.00	13.19	C
ATOM	784	CZ2	TRP	A	95	21.670	49.722	-9.891	1.00	11.91	C
ATOM	785	N	VAL	A	96	20.084	53.363	-2.801	1.00	10.54	N
ATOM	786	CA	VAL	A	96	20.513	53.688	-1.444	1.00	10.32	C
ATOM	787	C	VAL	A	96	21.142	52.452	-0.839	1.00	11.89	C
ATOM	788	O	VAL	A	96	20.511	51.404	-0.775	1.00	12.61	O
ATOM	789	CB	VAL	A	96	19.357	54.169	-0.592	1.00	11.42	C
ATOM	790	CG1	VAL	A	96	19.867	54.492	0.780	1.00	14.23	C
ATOM	791	CG2	VAL	A	96	18.719	55.422	-1.225	1.00	13.00	C
ATOM	792	N	LEU	A	97	22.391	52.556	-0.388	1.00	8.71	N
ATOM	793	CA	LEU	A	97	23.116	51.422	0.183	1.00	10.70	C
ATOM	794	C	LEU	A	97	22.986	51.457	1.712	1.00	10.07	C
ATOM	795	O	LEU	A	97	23.467	52.398	2.346	1.00	12.79	O
ATOM	796	CB	LEU	A	97	24.608	51.500	-0.135	1.00	11.16	C
ATOM	797	CG	LEU	A	97	24.997	51.138	-1.608	1.00	12.06	C
ATOM	798	CD1	LEU	A	97	24.306	51.952	-2.731	1.00	11.70	C
ATOM	799	CD2	LEU	A	97	26.521	51.215	-1.730	1.00	13.44	C
ATOM	800	N	MET	A	98	22.334	50.442	2.234	1.00	12.17	N
ATOM	801	CA	MET	A	98	22.039	50.383	3.668	1.00	11.44	C
ATOM	802	C	MET	A	98	22.786	49.232	4.354	1.00	10.59	C
ATOM	803	O	MET	A	98	23.012	48.184	3.796	1.00	12.17	O
ATOM	804	CB	MET	A	98	20.529	50.138	3.839	1.00	13.95	C
ATOM	805	CG	MET	A	98	19.666	51.320	3.245	1.00	15.96	C
ATOM	806	SD	MET	A	98	19.873	52.867	4.005	1.00	17.73	S
ATOM	807	CE	MET	A	98	19.467	52.512	5.821	1.00	14.01	C
ATOM	808	N	GLU	A	99	23.002	49.424	5.651	1.00	10.51	N
ATOM	809	CA	GLU	A	99	23.446	48.340	6.522	1.00	12.85	C
ATOM	810	C	GLU	A	99	22.388	47.190	6.464	1.00	13.14	C
ATOM	811	O	GLU	A	99	21.173	47.458	6.497	1.00	16.29	O
ATOM	812	CB	GLU	A	99	23.513	48.930	7.938	1.00	11.50	C
ATOM	813	CG	GLU	A	99	23.978	47.930	8.980	1.00	13.71	C
ATOM	814	CD	GLU	A	99	24.129	48.577	10.354	1.00	14.80	C
ATOM	815	OE1	GLU	A	99	23.869	49.794	10.534	1.00	14.64	O
ATOM	816	OE2	GLU	A	99	24.538	47.820	11.269	1.00	20.63	O
ATOM	817	N	PHE	A	100	22.836	45.933	6.370	1.00	15.63	N
ATOM	818	CA	PHE	A	100	21.921	44.810	6.215	1.00	17.57	C
ATOM	819	C	PHE	A	100	21.774	44.021	7.536	1.00	16.72	C
ATOM	820	O	PHE	A	100	22.795	43.549	8.083	1.00	20.12	O
ATOM	821	CB	PHE	A	100	22.528	43.913	5.161	1.00	20.23	C
ATOM	822	CG	PHE	A	100	21.805	42.626	4.976	1.00	22.59	C
ATOM	823	CD1	PHE	A	100	22.520	41.412	4.948	1.00	26.73	C
ATOM	824	CE1	PHE	A	100	21.844	40.202	4.750	1.00	25.39	C
ATOM	825	CZ	PHE	A	100	20.471	40.194	4.590	1.00	26.43	C
ATOM	826	CE2	PHE	A	100	19.757	41.397	4.624	1.00	26.96	C
ATOM	827	CD2	PHE	A	100	20.439	42.605	4.809	1.00	24.65	C
ATOM	828	N	LEU	A	101	20.563	43.960	8.094	1.00	18.25	N
ATOM	829	CA	LEU	A	101	20.353	43.356	9.407	1.00	18.61	C
ATOM	830	C	LEU	A	101	19.393	42.184	9.140	1.00	19.89	C
ATOM	831	O	LEU	A	101	18.500	42.308	8.268	1.00	21.24	O
ATOM	832	CB	LEU	A	101	19.656	44.318	10.379	1.00	20.99	C
ATOM	833	CG	LEU	A	101	20.524	45.270	11.230	1.00	23.61	C
ATOM	834	CD1	LEU	A	101	21.032	46.356	10.383	1.00	23.70	C
ATOM	835	CD2	LEU	A	101	19.701	45.885	12.379	1.00	24.57	C

FIGURE 4N

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ATOM    836  N   GLN A 102      19.551  41.073   9.868  1.00 19.23           N
ATOM    837  CA  GLN A 102      18.779  39.866   9.580  1.00 20.33           C
ATOM    838  C   GLN A 102      17.863  39.376  10.711  1.00 20.08           C
ATOM    839  O   GLN A 102      17.265  38.275  10.629  1.00 21.98           O
ATOM    840  CB  GLN A 102      19.727  38.730   9.188  1.00 21.58           C
ATOM    841  CG  GLN A 102      20.379  39.009   7.841  1.00 25.20           C
ATOM    842  CD  GLN A 102      21.359  37.908   7.455  1.00 28.51           C
ATOM    843  OE1 GLN A 102      20.941  36.873   6.951  1.00 30.63           O
ATOM    844  NE2 GLN A 102      22.652  38.151   7.677  1.00 25.83           N
ATOM    845  N   GLY A 103      17.760  40.146  11.781  1.00 20.33           N
ATOM    846  CA  GLY A 103      16.963  39.696  12.927  1.00 19.80           C
ATOM    847  C   GLY A 103      15.505  40.121  12.956  1.00 21.24           C
ATOM    848  O   GLY A 103      14.836  39.860  13.968  1.00 21.18           O
ATOM    849  N   GLY A 104      14.990  40.753  11.905  1.00 18.61           N
ATOM    850  CA  GLY A 104      13.564  41.066  11.840  1.00 18.70           C
ATOM    851  C   GLY A 104      13.307  42.394  12.540  1.00 19.18           C
ATOM    852  O   GLY A 104      14.262  43.057  12.938  1.00 19.97           O
ATOM    853  N   ALA A 105      12.038  42.760  12.640  1.00 16.72           N
ATOM    854  CA  ALA A 105      11.601  43.969  13.322  1.00 16.50           C
ATOM    855  C   ALA A 105      11.145  43.569  14.705  1.00 16.01           C
ATOM    856  O   ALA A 105      10.696  42.427  14.975  1.00 15.11           O
ATOM    857  CB  ALA A 105      10.500  44.607  12.582  1.00 17.50           C
ATOM    858  N   LEU A 106      11.223  44.534  15.606  1.00 13.34           N
ATOM    859  CA  LEU A 106      10.767  44.272  16.948  1.00 14.34           C
ATOM    860  C   LEU A 106       9.315  43.833  17.011  1.00 13.11           C
ATOM    861  O   LEU A 106       8.947  42.998  17.849  1.00 12.50           O
ATOM    862  CB  LEU A 106      10.991  45.535  17.785  1.00 13.09           C
ATOM    863  CG  LEU A 106      10.519  45.507  19.222  1.00 15.51           C
ATOM    864  CD1 LEU A 106      11.398  44.527  20.038  1.00 16.20           C
ATOM    865  CD2 LEU A 106      10.507  46.936  19.840  1.00 13.89           C
ATOM    866  N   THR A 107       8.496  44.360  16.114  1.00 11.69           N
ATOM    867  CA  THR A 107       7.080  44.016  16.042  1.00 13.42           C
ATOM    868  C   THR A 107       6.895  42.510  15.948  1.00 14.04           C
ATOM    869  O   THR A 107       5.912  42.004  16.454  1.00 14.96           O
ATOM    870  CB  THR A 107       6.471  44.591  14.811  1.00 15.46           C
ATOM    871  OG1 THR A 107       6.652  46.008  14.805  1.00 17.52           O
ATOM    872  CG2 THR A 107       4.938  44.422  14.879  1.00 17.25           C
ATOM    873  N   ASP A 108       7.820  41.827  15.284  1.00 14.15           N
ATOM    874  CA  ASP A 108       7.698  40.361  15.109  1.00 16.22           C
ATOM    875  C   ASP A 108       7.667  39.624  16.465  1.00 15.49           C
ATOM    876  O   ASP A 108       6.996  38.587  16.601  1.00 18.94           O
ATOM    877  CB  ASP A 108       8.901  39.792  14.309  1.00 19.52           C
ATOM    878  CG  ASP A 108       9.074  40.431  12.897  1.00 26.35           C
ATOM    879  OD1 ASP A 108       8.076  41.014  12.373  1.00 26.64           O
ATOM    880  OD2 ASP A 108      10.186  40.370  12.254  1.00 29.49           O
ATOM    881  N   ILE A 109       8.379  40.157  17.449  1.00 14.12           N
ATOM    882  CA  ILE A 109       8.395  39.523  18.779  1.00 12.58           C
ATOM    883  C   ILE A 109       7.299  40.179  19.637  1.00 14.03           C
ATOM    884  O   ILE A 109       6.542  39.477  20.294  1.00 14.42           O
ATOM    885  CB  ILE A 109       9.755  39.725  19.411  1.00 14.89           C
ATOM    886  CG1 ILE A 109      10.881  39.025  18.639  1.00 14.73           C
ATOM    887  CD1 ILE A 109      12.243  39.586  19.093  1.00 17.44           C
ATOM    888  CG2 ILE A 109       9.705  39.355  20.914  1.00 14.47           C
ATOM    889  N   VAL A 110       7.169  41.499  19.637  1.00 13.45           N
ATOM    890  CA  VAL A 110       6.271  42.132  20.616  1.00 14.46           C
ATOM    891  C   VAL A 110       4.789  41.918  20.321  1.00 13.96           C
ATOM    892  O   VAL A 110       3.955  41.987  21.191  1.00 14.33           O
ATOM    893  CB BVAL A 110       6.612  43.655  20.860  0.20 13.68           C
ATOM    894  CB AVAL A 110       6.615  43.651  20.865  0.80 15.82           C
ATOM    895  CG1BVAL A 110       6.986  44.373  19.601  0.20 13.60           C
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FIGURE 4O

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ATOM    896  CG1AVAL A 110       8.037  43.773  21.376  0.80 13.25           C
ATOM    897  CG2BVAL A 110       5.458  44.355  21.494  0.20  9.23           C
ATOM    898  CG2AVAL A 110       6.340  44.478  19.668  0.80 18.00           C
ATOM    899  N    SER A 111       4.476  41.576  19.083  1.00 14.00           N
ATOM    900  CA   SER A 111       3.108  41.251  18.722  1.00 15.03           C
ATOM    901  C    SER A 111       2.754  39.866  19.310  1.00 16.28           C
ATOM    902  O    SER A 111       1.558  39.547  19.477  1.00 19.72           O
ATOM    903  CB   SER A 111       2.890  41.168  17.192  1.00 16.85           C
ATOM    904  OG   SER A 111       3.677  40.164  16.557  1.00 18.09           O
ATOM    905  N    GLN A 112       3.774  39.074  19.608  1.00 12.16           N
ATOM    906  CA   GLN A 112       3.493  37.654  20.054  1.00 14.39           C
ATOM    907  C    GLN A 112       3.735  37.415  21.536  1.00 13.10           C
ATOM    908  O    GLN A 112       3.137  36.481  22.148  1.00 12.32           O
ATOM    909  CB   GLN A 112       4.447  36.732  19.317  1.00 14.74           C
ATOM    910  CG   GLN A 112       4.246  36.633  17.829  1.00 19.33           C
ATOM    911  CD   GLN A 112       2.871  36.139  17.496  1.00 29.23           C
ATOM    912  OE1  GLN A 112       2.476  35.032  17.885  1.00 31.05           O
ATOM    913  NE2  GLN A 112       2.099  36.984  16.793  1.00 35.47           N
ATOM    914  N    VAL A 113       4.690  38.155  22.089  1.00 11.18           N
ATOM    915  CA   VAL A 113       5.174  37.860  23.440  1.00 12.50           C
ATOM    916  C    VAL A 113       5.173  39.156  24.271  1.00 12.74           C
ATOM    917  O    VAL A 113       5.397  40.268  23.727  1.00 13.07           O
ATOM    918  CB BVAL A 113       6.569  37.210  23.476  0.35 12.64           C
ATOM    919  CB AVAL A 113       6.622  37.321  23.264  0.65 14.43           C
ATOM    920  CG1BVAL A 113       7.671  38.196  23.168  0.35  9.49           C
ATOM    921  CG1AVAL A 113       7.479  37.408  24.499  0.65 13.75           C
ATOM    922  CG2BVAL A 113       6.815  36.623  24.792  0.35 12.61           C
ATOM    923  CG2AVAL A 113       6.597  35.866  22.671  0.65 11.45           C
ATOM    924  N    ARG A 114       4.990  38.995  25.576  1.00 13.42           N
ATOM    925  CA   ARG A 114       5.169  40.085  26.526  1.00 13.22           C
ATOM    926  C    ARG A 114       6.594  40.016  27.072  1.00 13.70           C
ATOM    927  O    ARG A 114       6.975  39.124  27.916  1.00 17.07           O
ATOM    928  CB   ARG A 114       4.171  39.973  27.705  1.00 14.53           C
ATOM    929  CG   ARG A 114       2.761  39.897  27.218  1.00 12.79           C
ATOM    930  CD   ARG A 114       2.236  41.222  26.526  1.00 13.98           C
ATOM    931  NE   ARG A 114       2.475  41.210  25.057  1.00 17.63           N
ATOM    932  CZ   ARG A 114       1.727  40.551  24.168  1.00 17.46           C
ATOM    933  NH1  ARG A 114       0.647  39.829  24.543  1.00 22.66           N
ATOM    934  NH2  ARG A 114       2.031  40.550  22.886  1.00 18.52           N
ATOM    935  N    LEU A 115       7.439  40.935  26.629  1.00 14.08           N
ATOM    936  CA   LEU A 115       8.831  40.947  27.105  1.00 12.65           C
ATOM    937  C    LEU A 115       8.898  41.228  28.620  1.00 12.48           C
ATOM    938  O    LEU A 115       8.058  41.912  29.158  1.00 14.22           O
ATOM    939  CB   LEU A 115       9.650  42.025  26.392  1.00 13.13           C
ATOM    940  CG   LEU A 115       9.763  41.876  24.875  1.00 13.97           C
ATOM    941  CD1  LEU A 115      10.551  43.147  24.410  1.00 17.02           C
ATOM    942  CD2  LEU A 115      10.514  40.606  24.508  1.00 17.74           C
ATOM    943  N    ASN A 116       9.932  40.695  29.254  1.00 11.88           N
ATOM    944  CA   ASN A 116      10.060  40.986  30.671  1.00 13.02           C
ATOM    945  C    ASN A 116      10.815  42.310  30.824  1.00 13.59           C
ATOM    946  O    ASN A 116      11.244  42.912  29.813  1.00 13.07           O
ATOM    947  CB   ASN A 116      10.755  39.840  31.395  1.00 16.25           C
ATOM    948  CG   ASN A 116      12.178  39.630  30.919  1.00 16.11           C
ATOM    949  OD1  ASN A 116      12.912  40.583  30.657  1.00 16.01           O
ATOM    950  ND2  ASN A 116      12.584  38.368  30.826  1.00 21.99           N
ATOM    951  N    GLU A 117      10.992  42.764  32.058  1.00 12.79           N
ATOM    952  CA   GLU A 117      11.524  44.107  32.248  1.00 14.09           C
ATOM    953  C    GLU A 117      12.974  44.282  31.789  1.00 13.32           C
ATOM    954  O    GLU A 117      13.362  45.371  31.286  1.00 13.03           O
ATOM    955  CB   GLU A 117      11.301  44.616  33.687  1.00 16.70           C
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FIGURE 4P

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ATOM    956  CG  GLU A 117       9.822  44.855  33.942  1.00 17.78           C
ATOM    957  CD  GLU A 117       9.496  45.727  35.155  1.00 22.57           C
ATOM    958  OE1 GLU A 117      10.415  46.413  35.663  1.00 21.12           O
ATOM    959  OE2 GLU A 117       8.280  45.740  35.514  1.00 20.72           O
ATOM    960  N   GLU A 118      13.805  43.246  31.966  1.00 13.65           N
ATOM    961  CA  GLU A 118      15.185  43.297  31.493  1.00 13.25           C
ATOM    962  C   GLU A 118      15.205  43.439  29.944  1.00 12.90           C
ATOM    963  O   GLU A 118      15.994  44.230  29.403  1.00 13.31           O
ATOM    964  CB  GLU A 118      15.930  42.022  31.923  1.00 15.38           C
ATOM    965  CG  GLU A 118      17.316  41.891  31.323  1.00 19.94           C
ATOM    966  CD  GLU A 118      18.054  40.623  31.761  1.00 30.39           C
ATOM    967  OE1 GLU A 118      17.496  39.489  31.672  1.00 34.33           O
ATOM    968  OE2 GLU A 118      19.224  40.779  32.143  1.00 34.76           O
ATOM    969  N   GLN A 119      14.334  42.696  29.268  1.00 12.94           N
ATOM    970  CA  GLN A 119      14.252  42.787  27.785  1.00 11.65           C
ATOM    971  C   GLN A 119      13.730  44.154  27.340  1.00 12.55           C
ATOM    972  O   GLN A 119      14.241  44.771  26.374  1.00 11.34           O
ATOM    973  CB  GLN A 119      13.317  41.695  27.264  1.00 13.15           C
ATOM    974  CG  GLN A 119      13.969  40.277  27.440  1.00 13.95           C
ATOM    975  CD  GLN A 119      13.001  39.129  27.285  1.00 15.25           C
ATOM    976  OE1 GLN A 119      11.797  39.235  27.605  1.00 16.66           O
ATOM    977  NE2 GLN A 119      13.523  37.999  26.756  1.00 19.76           N
ATOM    978  N   ILE A 120      12.717  44.654  28.044  1.00 10.51           N
ATOM    979  CA  ILE A 120      12.262  46.026  27.757  1.00 10.70           C
ATOM    980  C   ILE A 120      13.369  47.045  27.916  1.00 11.15           C
ATOM    981  O   ILE A 120      13.542  47.935  27.036  1.00 11.61           O
ATOM    982  CB  ILE A 120      10.996  46.368  28.587  1.00 10.60           C
ATOM    983  CG1 ILE A 120       9.854  45.455  28.172  1.00 12.60           C
ATOM    984  CD1 ILE A 120       8.564  45.667  29.005  1.00 13.91           C
ATOM    985  CG2 ILE A 120      10.604  47.889  28.445  1.00 10.56           C
ATOM    986  N   ALA A 121      14.123  46.968  29.015  1.00 11.01           N
ATOM    987  CA  ALA A 121      15.204  47.921  29.276  1.00 10.58           C
ATOM    988  C   ALA A 121      16.260  47.791  28.170  1.00 11.46           C
ATOM    989  O   ALA A 121      16.842  48.772  27.763  1.00 12.49           O
ATOM    990  CB  ALA A 121      15.809  47.618  30.670  1.00 10.64           C
ATOM    991  N   THR A 122      16.523  46.568  27.688  1.00 12.37           N
ATOM    992  CA  THR A 122      17.567  46.410  26.680  1.00 13.42           C
ATOM    993  C   THR A 122      17.115  47.147  25.395  1.00 11.43           C
ATOM    994  O   THR A 122      17.910  47.873  24.736  1.00 13.23           O
ATOM    995  CB  THR A 122      17.699  44.933  26.395  1.00 14.45           C
ATOM    996  OG1 THR A 122      18.243  44.306  27.568  1.00 18.68           O
ATOM    997  CG2 THR A 122      18.716  44.685  25.259  1.00 17.22           C
ATOM    998  N   VAL A 123      15.818  47.003  25.066  1.00  8.58           N
ATOM    999  CA  VAL A 123      15.303  47.707  23.861  1.00  9.31           C
ATOM   1000  C   VAL A 123      15.329  49.203  24.073  1.00 10.75           C
ATOM   1001  O   VAL A 123      15.818  49.976  23.213  1.00 10.05           O
ATOM   1002  CB  VAL A 123      13.913  47.274  23.522  1.00 12.89           C
ATOM   1003  CG1 VAL A 123      13.324  48.101  22.408  1.00 12.01           C
ATOM   1004  CG2 VAL A 123      13.923  45.811  23.127  1.00 12.38           C
ATOM   1005  N   CYS A 124      14.773  49.636  25.204  1.00  9.98           N
ATOM   1006  CA  CYS A 124      14.736  51.059  25.488  1.00 11.10           C
ATOM   1007  C   CYS A 124      16.090  51.731  25.543  1.00 11.85           C
ATOM   1008  O   CYS A 124      16.248  52.864  25.007  1.00 12.25           O
ATOM   1009  CB  CYS A 124      14.010  51.291  26.817  1.00 13.17           C
ATOM   1010  SG  CYS A 124      12.233  51.061  26.610  1.00 21.75           S
ATOM   1011  N   GLU A 125      17.066  51.098  26.189  1.00 11.05           N
ATOM   1012  CA  GLU A 125      18.381  51.711  26.272  1.00 12.60           C
ATOM   1013  C   GLU A 125      18.982  51.901  24.871  1.00 12.30           C
ATOM   1014  O   GLU A 125      19.557  52.952  24.578  1.00 11.09           O
ATOM   1015  CB  GLU A 125      19.288  50.853  27.129  1.00 14.58           C
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FIGURE 4Q

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ATOM   1016  CG  GLU A 125      20.574  51.581  27.491  1.00 18.53           C
ATOM   1017  CD  GLU A 125      21.721  51.337  26.561  1.00 27.54           C
ATOM   1018  OE1 GLU A 125      22.764  52.003  26.829  1.00 34.34           O
ATOM   1019  OE2 GLU A 125      21.658  50.527  25.580  1.00 30.51           O
ATOM   1020  N   ALA A 126      18.798  50.897  23.995  1.00  9.99           N
ATOM   1021  CA  ALA A 126      19.358  51.057  22.661  1.00 11.65           C
ATOM   1022  C   ALA A 126      18.708  52.196  21.884  1.00 10.07           C
ATOM   1023  O   ALA A 126      19.410  53.039  21.271  1.00 10.91           O
ATOM   1024  CB  ALA A 126      19.276  49.706  21.918  1.00 12.17           C
ATOM   1025  N   VAL A 127      17.368  52.230  21.914  1.00  9.33           N
ATOM   1026  CA  VAL A 127      16.635  53.312  21.227  1.00 11.04           C
ATOM   1027  C   VAL A 127      16.995  54.683  21.776  1.00 10.47           C
ATOM   1028  O   VAL A 127      17.197  55.639  21.018  1.00  9.96           O
ATOM   1029  CB  VAL A 127      15.091  53.106  21.274  1.00 11.82           C
ATOM   1030  CG1 VAL A 127      14.347  54.254  20.562  1.00 14.40           C
ATOM   1031  CG2 VAL A 127      14.804  51.749  20.632  1.00 13.92           C
ATOM   1032  N   LEU A 128      17.171  54.746  23.083  1.00  8.83           N
ATOM   1033  CA  LEU A 128      17.474  56.025  23.714  1.00 10.84           C
ATOM   1034  C   LEU A 128      18.893  56.513  23.439  1.00  9.60           C
ATOM   1035  O   LEU A 128      19.114  57.695  23.361  1.00 11.82           O
ATOM   1036  CB  LEU A 128      17.216  55.917  25.222  1.00  9.40           C
ATOM   1037  CG  LEU A 128      15.698  56.031  25.513  1.00 10.65           C
ATOM   1038  CD1 LEU A 128      15.467  55.525  26.964  1.00 11.89           C
ATOM   1039  CD2 LEU A 128      15.140  57.454  25.350  1.00 10.29           C
ATOM   1040  N   GLN A 129      19.808  55.555  23.275  1.00  9.77           N
ATOM   1041  CA  GLN A 129      21.185  55.944  22.883  1.00 12.07           C
ATOM   1042  C   GLN A 129      21.111  56.551  21.480  1.00 11.57           C
ATOM   1043  O   GLN A 129      21.743  57.601  21.246  1.00 11.49           O
ATOM   1044  CB  GLN A 129      22.133  54.743  22.864  1.00 11.08           C
ATOM   1045  CG  GLN A 129      22.500  54.232  24.258  1.00 13.59           C
ATOM   1046  CD  GLN A 129      23.396  55.167  25.085  1.00 20.05           C
ATOM   1047  OE1 GLN A 129      23.883  56.220  24.620  1.00 21.69           O
ATOM   1048  NE2 GLN A 129      23.612  54.764  26.349  1.00 22.68           N
ATOM   1049  N   ALA A 130      20.366  55.905  20.562  1.00  9.60           N
ATOM   1050  CA  ALA A 130      20.193  56.500  19.227  1.00 10.55           C
ATOM   1051  C   ALA A 130      19.541  57.865  19.329  1.00 11.18           C
ATOM   1052  O   ALA A 130      19.983  58.783  18.673  1.00  9.99           O
ATOM   1053  CB  ALA A 130      19.289  55.613  18.389  1.00 11.03           C
ATOM   1054  N   LEU A 131      18.440  57.982  20.101  1.00  9.86           N
ATOM   1055  CA  LEU A 131      17.715  59.267  20.132  1.00 11.73           C
ATOM   1056  C   LEU A 131      18.551  60.354  20.831  1.00 10.68           C
ATOM   1057  O   LEU A 131      18.490  61.531  20.430  1.00 12.36           O
ATOM   1058  CB  LEU A 131      16.342  59.123  20.818  1.00 10.06           C
ATOM   1059  CG  LEU A 131      15.315  58.296  20.058  1.00 11.70           C
ATOM   1060  CD1 LEU A 131      14.019  58.206  20.940  1.00 13.25           C
ATOM   1061  CD2 LEU A 131      14.988  58.876  18.660  1.00 12.48           C
ATOM   1062  N   ALA A 132      19.285  60.016  21.885  1.00 10.23           N
ATOM   1063  CA  ALA A 132      20.089  61.034  22.526  1.00 12.26           C
ATOM   1064  C   ALA A 132      21.138  61.598  21.531  1.00 13.96           C
ATOM   1065  O   ALA A 132      21.355  62.791  21.492  1.00 14.29           O
ATOM   1066  CB  ALA A 132      20.729  60.513  23.780  1.00 14.33           C
ATOM   1067  N   TYR A 133      21.704  60.720  20.695  1.00 11.05           N
ATOM   1068  CA  TYR A 133      22.659  61.221  19.697  1.00 11.87           C
ATOM   1069  C   TYR A 133      21.934  62.028  18.610  1.00 11.09           C
ATOM   1070  O   TYR A 133      22.345  63.138  18.302  1.00 12.95           O
ATOM   1071  CB  TYR A 133      23.327  59.995  19.048  1.00 11.95           C
ATOM   1072  CG  TYR A 133      24.049  60.316  17.758  1.00 13.87           C
ATOM   1073  CD1 TYR A 133      25.280  60.927  17.782  1.00 17.00           C
ATOM   1074  CE1 TYR A 133      25.962  61.218  16.562  1.00 13.99           C
ATOM   1075  CZ  TYR A 133      25.389  60.899  15.362  1.00 16.47           C
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FIGURE 4R

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ATOM   1076  OH  TYR A 133      26.060  61.202  14.166  1.00 17.81           O
ATOM   1077  CE2 TYR A 133      24.146  60.298  15.294  1.00 16.35           C
ATOM   1078  CD2 TYR A 133      23.472  59.992  16.529  1.00 16.98           C
ATOM   1079  N   LEU A 134      20.841  61.498  18.074  1.00  9.47           N
ATOM   1080  CA  LEU A 134      20.146  62.211  17.011  1.00 10.45           C
ATOM   1081  C   LEU A 134      19.607  63.569  17.506  1.00  9.46           C
ATOM   1082  O   LEU A 134      19.713  64.570  16.803  1.00  8.97           O
ATOM   1083  CB  LEU A 134      18.986  61.378  16.461  1.00 10.59           C
ATOM   1084  CG  LEU A 134      19.390  60.088  15.671  1.00 13.02           C
ATOM   1085  CD1 LEU A 134      18.117  59.366  15.470  1.00 17.36           C
ATOM   1086  CD2 LEU A 134      20.068  60.420  14.337  1.00 15.31           C
ATOM   1087  N   HIS A 135      18.974  63.598  18.694  1.00  9.56           N
ATOM   1088  CA  HIS A 135      18.362  64.855  19.167  1.00  8.61           C
ATOM   1089  C   HIS A 135      19.442  65.910  19.447  1.00 11.06           C
ATOM   1090  O   HIS A 135      19.190  67.096  19.208  1.00 11.37           O
ATOM   1091  CB  HIS A 135      17.569  64.593  20.429  1.00  8.92           C
ATOM   1092  CG  HIS A 135      16.299  63.823  20.243  1.00  9.30           C
ATOM   1093  ND1 HIS A 135      15.760  63.385  19.029  1.00 11.41           N
ATOM   1094  CE1 HIS A 135      14.617  62.724  19.257  1.00  4.33           C
ATOM   1095  NE2 HIS A 135      14.460  62.662  20.574  1.00 10.92           N
ATOM   1096  CD2 HIS A 135      15.512  63.295  21.207  1.00  4.45           C
ATOM   1097  N   ALA A 136      20.615  65.465  19.884  1.00 11.25           N
ATOM   1098  CA  ALA A 136      21.706  66.411  20.124  1.00 13.83           C
ATOM   1099  C   ALA A 136      22.157  67.029  18.794  1.00 15.27           C
ATOM   1100  O   ALA A 136      22.751  68.103  18.790  1.00 16.71           O
ATOM   1101  CB  ALA A 136      22.886  65.666  20.784  1.00 14.20           C
ATOM   1102  N   GLN A 137      21.949  66.337  17.683  1.00 11.54           N
ATOM   1103  CA  GLN A 137      22.295  66.900  16.378  1.00 14.15           C
ATOM   1104  C   GLN A 137      21.189  67.700  15.758  1.00 13.56           C
ATOM   1105  O   GLN A 137      21.338  68.246  14.642  1.00 15.91           O
ATOM   1106  CB  GLN A 137      22.698  65.761  15.397  1.00 12.79           C
ATOM   1107  CG  GLN A 137      23.845  64.869  15.910  1.00 17.58           C
ATOM   1108  CD  GLN A 137      25.051  65.726  16.199  1.00 26.69           C
ATOM   1109  OE1 GLN A 137      25.471  66.464  15.339  1.00 28.56           O
ATOM   1110  NE2 GLN A 137      25.540  65.700  17.407  1.00 33.40           N
ATOM   1111  N   GLY A 138      20.026  67.730  16.401  1.00 10.42           N
ATOM   1112  CA  GLY A 138      18.814  68.377  15.872  1.00 10.42           C
ATOM   1113  C   GLY A 138      17.966  67.535  14.915  1.00 10.09           C
ATOM   1114  O   GLY A 138      17.151  68.068  14.153  1.00 12.40           O
ATOM   1115  N   VAL A 139      18.163  66.213  14.940  1.00  9.19           N
ATOM   1116  CA  VAL A 139      17.370  65.368  14.097  1.00  8.77           C
ATOM   1117  C   VAL A 139      16.173  64.854  14.886  1.00  9.95           C
ATOM   1118  O   VAL A 139      16.379  64.338  16.011  1.00 10.76           O
ATOM   1119  CB  VAL A 139      18.196  64.171  13.579  1.00  9.06           C
ATOM   1120  CG1 VAL A 139      17.301  63.283  12.734  1.00 10.36           C
ATOM   1121  CG2 VAL A 139      19.375  64.725  12.704  1.00 10.69           C
ATOM   1122  N   ILE A 140      14.980  64.973  14.279  1.00  9.20           N
ATOM   1123  CA  ILE A 140      13.752  64.365  14.822  1.00  7.17           C
ATOM   1124  C   ILE A 140      13.357  63.214  13.920  1.00  7.49           C
ATOM   1125  O   ILE A 140      13.270  63.378  12.727  1.00  8.88           O
ATOM   1126  CB  ILE A 140      12.600  65.368  14.877  1.00  8.02           C
ATOM   1127  CG1 ILE A 140      13.089  66.760  15.341  1.00 12.50           C
ATOM   1128  CD1 ILE A 140      11.964  67.797  15.176  1.00 12.44           C
ATOM   1129  CG2 ILE A 140      11.477  64.797  15.824  1.00 11.12           C
ATOM   1130  N   HIS A 141      13.109  62.067  14.507  1.00  7.87           N
ATOM   1131  CA  HIS A 141      12.819  60.886  13.654  1.00  6.03           C
ATOM   1132  C   HIS A 141      11.374  60.937  13.144  1.00  7.50           C
ATOM   1133  O   HIS A 141      11.113  60.735  11.943  1.00  8.21           O
ATOM   1134  CB  HIS A 141      13.058  59.635  14.508  1.00  8.33           C
ATOM   1135  CG  HIS A 141      12.795  58.362  13.763  1.00  8.10           C
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FIGURE 4S

ATOM	1136	ND1	HIS	A	141	11.537	57.884	13.505	1.00	8.17	N
ATOM	1137	CE1	HIS	A	141	11.625	56.727	12.869	1.00	10.41	C
ATOM	1138	NE2	HIS	A	141	12.914	56.456	12.664	1.00	9.43	N
ATOM	1139	CD2	HIS	A	141	13.663	57.446	13.242	1.00	10.16	C
ATOM	1140	N	ARG	A	142	10.434	61.155	14.066	1.00	7.54	N
ATOM	1141	CA	ARG	A	142	9.028	61.421	13.769	1.00	7.41	C
ATOM	1142	C	ARG	A	142	8.201	60.196	13.394	1.00	9.29	C
ATOM	1143	O	ARG	A	142	6.966	60.333	13.154	1.00	10.59	O
ATOM	1144	CB	ARG	A	142	8.780	62.549	12.720	1.00	8.27	C
ATOM	1145	CG	ARG	A	142	9.477	63.832	13.191	1.00	9.10	C
ATOM	1146	CD	ARG	A	142	8.944	65.110	12.507	1.00	9.42	C
ATOM	1147	NE	ARG	A	142	9.181	65.052	11.064	1.00	8.94	N
ATOM	1148	CZ	ARG	A	142	8.923	66.088	10.283	1.00	9.87	C
ATOM	1149	NH1	ARG	A	142	9.200	66.030	8.976	1.00	12.02	N
ATOM	1150	NH2	ARG	A	142	8.336	67.162	10.803	1.00	10.46	N
ATOM	1151	N	ASP	A	143	8.824	59.026	13.407	1.00	7.57	N
ATOM	1152	CA	ASP	A	143	8.023	57.801	13.145	1.00	8.88	C
ATOM	1153	C	ASP	A	143	8.442	56.632	13.987	1.00	10.57	C
ATOM	1154	O	ASP	A	143	8.513	55.482	13.489	1.00	12.58	O
ATOM	1155	CB	ASP	A	143	8.002	57.503	11.632	1.00	11.13	C
ATOM	1156	CG	ASP	A	143	6.764	56.723	11.212	1.00	18.83	C
ATOM	1157	OD1	ASP	A	143	5.776	56.605	12.004	1.00	17.51	O
ATOM	1158	OD2	ASP	A	143	6.743	56.154	10.072	1.00	20.61	O
ATOM	1159	N	ILE	A	144	8.683	56.896	15.290	1.00	10.10	N
ATOM	1160	CA	ILE	A	144	9.100	55.832	16.210	1.00	9.71	C
ATOM	1161	C	ILE	A	144	7.882	54.910	16.530	1.00	11.44	C
ATOM	1162	O	ILE	A	144	6.779	55.385	16.846	1.00	10.40	O
ATOM	1163	CB	ILE	A	144	9.662	56.452	17.514	1.00	11.81	C
ATOM	1164	CG1B	ILE	A	144	10.926	57.236	17.117	0.35	10.81	C
ATOM	1165	CG1A	ILE	A	144	10.943	57.284	17.241	0.65	12.58	C
ATOM	1166	CD1B	ILE	A	144	11.635	57.844	18.199	0.35	9.54	C
ATOM	1167	CD1A	ILE	A	144	12.122	56.415	16.843	0.65	15.04	C
ATOM	1168	CG2	ILE	A	144	9.934	55.350	18.559	1.00	12.62	C
ATOM	1169	N	LYS	A	145	8.090	53.602	16.360	1.00	9.50	N
ATOM	1170	CA	LYS	A	145	7.082	52.559	16.692	1.00	9.17	C
ATOM	1171	C	LYS	A	145	7.804	51.250	16.566	1.00	10.72	C
ATOM	1172	O	LYS	A	145	8.917	51.209	16.025	1.00	9.64	O
ATOM	1173	CB	LYS	A	145	5.942	52.610	15.707	1.00	10.43	C
ATOM	1174	CG	LYS	A	145	6.379	52.552	14.271	1.00	11.59	C
ATOM	1175	CD	LYS	A	145	5.155	52.746	13.355	1.00	17.86	C
ATOM	1176	CE	LYS	A	145	5.526	53.157	11.919	1.00	23.57	C
ATOM	1177	NZ	LYS	A	145	6.741	52.617	11.308	1.00	26.05	N
ATOM	1178	N	SER	A	146	7.176	50.139	16.981	1.00	11.26	N
ATOM	1179	CA	SER	A	146	7.930	48.908	17.042	1.00	11.22	C
ATOM	1180	C	SER	A	146	8.431	48.424	15.721	1.00	11.43	C
ATOM	1181	O	SER	A	146	9.457	47.733	15.689	1.00	12.31	O
ATOM	1182	CB	SER	A	146	7.032	47.781	17.660	1.00	10.91	C
ATOM	1183	OG	SER	A	146	5.827	47.616	16.911	1.00	14.55	O
ATOM	1184	N	ASP	A	147	7.758	48.778	14.632	1.00	10.74	N
ATOM	1185	CA	ASP	A	147	8.286	48.268	13.378	1.00	13.24	C
ATOM	1186	C	ASP	A	147	9.360	49.125	12.759	1.00	13.38	C
ATOM	1187	O	ASP	A	147	9.921	48.691	11.764	1.00	16.42	O
ATOM	1188	CB	ASP	A	147	7.215	47.753	12.412	1.00	19.10	C
ATOM	1189	CG	ASP	A	147	6.612	48.811	11.618	1.00	22.88	C
ATOM	1190	OD1	ASP	A	147	6.596	49.992	12.051	1.00	26.77	O
ATOM	1191	OD2	ASP	A	147	6.089	48.525	10.492	1.00	31.82	O
ATOM	1192	N	SER	A	148	9.730	50.234	13.437	1.00	11.24	N
ATOM	1193	CA	SER	A	148	10.865	51.085	13.035	1.00	11.41	C
ATOM	1194	C	SER	A	148	12.139	50.555	13.722	1.00	12.41	C
ATOM	1195	O	SER	A	148	13.221	51.082	13.532	1.00	11.93	O

FIGURE 4T

```
ATOM   1196  CB  SER A 148      10.616  52.571  13.462  1.00 13.47           C
ATOM   1197  OG  SER A 148       9.510  53.075  12.756  1.00 18.49           O
ATOM   1198  N   ILE A 149      12.012  49.565  14.603  1.00 10.17           N
ATOM   1199  CA  ILE A 149      13.138  49.082  15.390  1.00  9.25           C
ATOM   1200  C   ILE A 149      13.560  47.734  14.780  1.00 11.79           C
ATOM   1201  O   ILE A 149      12.711  46.816  14.679  1.00 13.50           O
ATOM   1202  CB  ILE A 149      12.719  48.879  16.846  1.00 10.26           C
ATOM   1203  CG1 ILE A 149      12.195  50.215  17.445  1.00 11.46           C
ATOM   1204  CD1 ILE A 149      13.149  51.331  17.249  1.00 13.52           C
ATOM   1205  CG2 ILE A 149      13.915  48.281  17.639  1.00 13.68           C
ATOM   1206  N   LEU A 150      14.836  47.618  14.366  1.00 11.05           N
ATOM   1207  CA  LEU A 150      15.293  46.371  13.706  1.00 10.73           C
ATOM   1208  C   LEU A 150      16.269  45.659  14.615  1.00 12.50           C
ATOM   1209  O   LEU A 150      16.952  46.299  15.430  1.00 14.29           O
ATOM   1210  CB  LEU A 150      15.998  46.711  12.381  1.00 12.10           C
ATOM   1211  CG  LEU A 150      15.081  47.364  11.321  1.00 15.53           C
ATOM   1212  CD1 LEU A 150      15.794  47.476   9.917  1.00 18.62           C
ATOM   1213  CD2 LEU A 150      13.705  46.699  11.169  1.00 20.40           C
ATOM   1214  N   LEU A 151      16.378  44.341  14.472  1.00 15.80           N
ATOM   1215  CA  LEU A 151      17.277  43.604  15.345  1.00 17.22           C
ATOM   1216  C   LEU A 151      18.331  42.877  14.516  1.00 16.07           C
ATOM   1217  O   LEU A 151      18.090  42.515  13.339  1.00 15.72           O
ATOM   1218  CB  LEU A 151      16.466  42.574  16.094  1.00 17.53           C
ATOM   1219  CG  LEU A 151      15.249  43.116  16.847  1.00 20.60           C
ATOM   1220  CD1 LEU A 151      14.379  42.026  17.314  1.00 25.61           C
ATOM   1221  CD2 LEU A 151      15.701  43.953  18.018  1.00 24.59           C
ATOM   1222  N   THR A 152      19.484  42.690  15.106  1.00 17.59           N
ATOM   1223  CA  THR A 152      20.493  41.843  14.454  1.00 17.17           C
ATOM   1224  C   THR A 152      20.303  40.429  14.974  1.00 20.42           C
ATOM   1225  O   THR A 152      19.555  40.160  15.964  1.00 16.52           O
ATOM   1226  CB  THR A 152      21.894  42.310  14.703  1.00 19.53           C
ATOM   1227  OG1 THR A 152      22.208  42.106  16.082  1.00 19.31           O
ATOM   1228  CG2 THR A 152      22.071  43.851  14.412  1.00 19.23           C
ATOM   1229  N   LEU A 153      20.975  39.485  14.309  1.00 19.93           N
ATOM   1230  CA  LEU A 153      20.793  38.079  14.714  1.00 21.52           C
ATOM   1231  C   LEU A 153      21.415  37.852  16.058  1.00 20.48           C
ATOM   1232  O   LEU A 153      20.977  36.943  16.790  1.00 21.14           O
ATOM   1233  CB  LEU A 153      21.396  37.131  13.692  1.00 21.93           C
ATOM   1234  CG  LEU A 153      20.468  36.957  12.485  1.00 24.45           C
ATOM   1235  CD1 LEU A 153      21.186  36.112  11.443  1.00 29.58           C
ATOM   1236  CD2 LEU A 153      19.117  36.317  12.829  1.00 24.29           C
ATOM   1237  N   ASP A 154      22.412  38.675  16.396  1.00 19.37           N
ATOM   1238  CA  ASP A 154      23.048  38.628  17.718  1.00 21.62           C
ATOM   1239  C   ASP A 154      22.385  39.509  18.792  1.00 18.86           C
ATOM   1240  O   ASP A 154      22.952  39.650  19.892  1.00 21.52           O
ATOM   1241  CB  ASP A 154      24.583  38.906  17.631  1.00 22.62           C
ATOM   1242  CG  ASP A 154      24.926  40.377  17.296  1.00 32.83           C
ATOM   1243  OD1 ASP A 154      25.986  40.911  17.778  1.00 38.47           O
ATOM   1244  OD2 ASP A 154      24.214  41.088  16.564  1.00 35.75           O
ATOM   1245  N   GLY A 155      21.209  40.090  18.478  1.00 16.18           N
ATOM   1246  CA  GLY A 155      20.380  40.763  19.476  1.00 15.22           C
ATOM   1247  C   GLY A 155      20.655  42.244  19.696  1.00 16.46           C
ATOM   1248  O   GLY A 155      20.243  42.842  20.700  1.00 18.18           O
ATOM   1249  N   ARG A 156      21.344  42.877  18.749  1.00 15.57           N
ATOM   1250  CA  ARG A 156      21.566  44.314  18.820  1.00 17.47           C
ATOM   1251  C   ARG A 156      20.297  44.970  18.258  1.00 14.35           C
ATOM   1252  O   ARG A 156      19.590  44.398  17.416  1.00 14.49           O
ATOM   1253  CB  ARG A 156      22.775  44.689  17.962  1.00 19.38           C
ATOM   1254  CG  ARG A 156      24.161  44.410  18.598  1.00 28.07           C
ATOM   1255  CD  ARG A 156      25.331  44.576  17.563  1.00 34.94           C
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FIGURE 4U

```
ATOM   1256  NE  ARG A 156      25.271  43.561  16.486  1.00 41.05           N
ATOM   1257  CZ  ARG A 156      25.484  43.749  15.168  1.00 40.30           C
ATOM   1258  NH1 ARG A 156      25.800  44.943  14.642  1.00 41.17           N
ATOM   1259  NH2 ARG A 156      25.380  42.702  14.354  1.00 39.14           N
ATOM   1260  N   VAL A 157      19.989  46.128  18.772  1.00 12.09           N
ATOM   1261  CA  VAL A 157      18.725  46.802  18.485  1.00 11.18           C
ATOM   1262  C   VAL A 157      19.082  48.102  17.817  1.00 10.05           C
ATOM   1263  O   VAL A 157      19.878  48.875  18.346  1.00 11.59           O
ATOM   1264  CB  VAL A 157      17.986  47.123  19.838  1.00 10.36           C
ATOM   1265  CG1 VAL A 157      16.763  47.987  19.636  1.00 10.99           C
ATOM   1266  CG2 VAL A 157      17.595  45.790  20.526  1.00 12.24           C
ATOM   1267  N   LYS A 158      18.495  48.329  16.649  1.00 10.46           N
ATOM   1268  CA  LYS A 158      18.775  49.561  15.909  1.00  8.94           C
ATOM   1269  C   LYS A 158      17.541  50.239  15.375  1.00 10.28           C
ATOM   1270  O   LYS A 158      16.556  49.584  14.977  1.00 12.90           O
ATOM   1271  CB  LYS A 158      19.704  49.254  14.726  1.00  9.69           C
ATOM   1272  CG  LYS A 158      20.985  48.537  15.164  1.00  9.09           C
ATOM   1273  CD  LYS A 158      22.092  48.703  14.091  1.00 10.47           C
ATOM   1274  CE  LYS A 158      23.305  47.829  14.454  1.00 15.71           C
ATOM   1275  NZ  LYS A 158      24.582  48.494  13.909  1.00 18.73           N
ATOM   1276  N   LEU A 159      17.622  51.551  15.275  1.00  9.03           N
ATOM   1277  CA  LEU A 159      16.517  52.374  14.804  1.00  8.17           C
ATOM   1278  C   LEU A 159      16.645  52.553  13.294  1.00  9.55           C
ATOM   1279  O   LEU A 159      17.750  52.820  12.780  1.00 11.01           O
ATOM   1280  CB  LEU A 159      16.633  53.720  15.496  1.00 10.45           C
ATOM   1281  CG  LEU A 159      15.619  54.779  15.080  1.00 11.72           C
ATOM   1282  CD1 LEU A 159      14.156  54.252  15.329  1.00 12.28           C
ATOM   1283  CD2 LEU A 159      15.913  56.012  15.969  1.00 15.76           C
ATOM   1284  N   SER A 160      15.551  52.390  12.578  1.00  8.93           N
ATOM   1285  CA  SER A 160      15.548  52.553  11.140  1.00 10.21           C
ATOM   1286  C   SER A 160      14.340  53.386  10.700  1.00 11.85           C
ATOM   1287  O   SER A 160      13.665  54.015  11.521  1.00  9.82           O
ATOM   1288  CB BSER A 160      15.490  51.174  10.517  0.35 11.55           C
ATOM   1289  CB ASER A 160      15.598  51.211  10.458  0.65 12.05           C
ATOM   1290  OG BSER A 160      14.241  50.573  10.792  0.35 13.78           O
ATOM   1291  OG ASER A 160      15.958  51.397   9.093  0.65 13.60           O
ATOM   1292  N   ASP A 161      14.044  53.363   9.406  1.00 13.47           N
ATOM   1293  CA  ASP A 161      12.812  53.983   8.829  1.00 13.87           C
ATOM   1294  C   ASP A 161      12.770  55.502   9.096  1.00 11.99           C
ATOM   1295  O   ASP A 161      11.822  56.039   9.709  1.00 12.87           O
ATOM   1296  CB  ASP A 161      11.525  53.321   9.298  1.00 16.18           C
ATOM   1297  CG  ASP A 161      11.345  51.900   8.704  1.00 26.14           C
ATOM   1298  OD1 ASP A 161      12.145  51.465   7.812  1.00 29.71           O
ATOM   1299  OD2 ASP A 161      10.423  51.153   9.067  1.00 29.86           O
ATOM   1300  N   PHE A 162      13.776  56.172   8.563  1.00 11.14           N
ATOM   1301  CA  PHE A 162      13.920  57.621   8.705  1.00 12.81           C
ATOM   1302  C   PHE A 162      13.202  58.454   7.645  1.00 12.24           C
ATOM   1303  O   PHE A 162      13.478  59.682   7.528  1.00 13.50           O
ATOM   1304  CB  PHE A 162      15.418  57.974   8.697  1.00 11.97           C
ATOM   1305  CG  PHE A 162      16.090  57.699  10.010  1.00  9.54           C
ATOM   1306  CD1 PHE A 162      16.457  56.387  10.399  1.00 13.00           C
ATOM   1307  CE1 PHE A 162      17.033  56.175  11.646  1.00 13.37           C
ATOM   1308  CZ  PHE A 162      17.290  57.265  12.483  1.00 12.40           C
ATOM   1309  CE2 PHE A 162      16.960  58.559  12.084  1.00 12.30           C
ATOM   1310  CD2 PHE A 162      16.352  58.751  10.863  1.00 11.27           C
ATOM   1311  N   GLY A 163      12.268  57.858   6.906  1.00 13.82           N
ATOM   1312  CA  GLY A 163      11.562  58.634   5.886  1.00 13.48           C
ATOM   1313  C   GLY A 163      10.914  59.976   6.279  1.00 14.52           C
ATOM   1314  O   GLY A 163      10.907  60.975   5.505  1.00 14.41           O
ATOM   1315  N   PHE A 164      10.450  60.062   7.525  1.00 11.20           N
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FIGURE 4V

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ATOM   1316  CA  PHE A 164       9.780  61.271   7.982  1.00 11.22           C
ATOM   1317  C   PHE A 164      10.683  62.157   8.793  1.00 10.65           C
ATOM   1318  O   PHE A 164      10.212  63.129   9.418  1.00 10.34           O
ATOM   1319  CB BPHE A 164       8.500  60.911   8.742  0.35 13.03           C
ATOM   1320  CB APHE A 164       8.604  60.908   8.893  0.65 13.79           C
ATOM   1321  CG BPHE A 164       7.525  60.088   7.925  0.35 15.59           C
ATOM   1322  CG APHE A 164       7.327  60.560   8.168  0.65 18.35           C
ATOM   1323  CD1BPHE A 164       7.727  58.744   7.727  0.35 17.23           C
ATOM   1324  CD1APHE A 164       6.498  59.550   8.676  0.65 20.64           C
ATOM   1325  CE1BPHE A 164       6.836  57.979   6.959  0.35 21.72           C
ATOM   1326  CE1APHE A 164       5.294  59.220   8.035  0.65 19.69           C
ATOM   1327  CZ BPHE A 164       5.720  58.586   6.414  0.35 20.85           C
ATOM   1328  CZ APHE A 164       4.913  59.926   6.883  0.65 22.80           C
ATOM   1329  CE2BPHE A 164       5.513  59.941   6.601  0.35 22.03           C
ATOM   1330  CE2APHE A 164       5.734  60.956   6.369  0.65 21.66           C
ATOM   1331  CD2BPHE A 164       6.415  60.684   7.360  0.35 20.62           C
ATOM   1332  CD2APHE A 164       6.928  61.270   7.032  0.65 19.72           C
ATOM   1333  N   CYS A 165      11.975  61.890   8.785  1.00  8.33           N
ATOM   1334  CA  CYS A 165      12.866  62.678   9.630  1.00  9.67           C
ATOM   1335  C   CYS A 165      12.967  64.172   9.233  1.00 10.06           C
ATOM   1336  O   CYS A 165      12.650  64.604   8.088  1.00 12.24           O
ATOM   1337  CB  CYS A 165      14.239  62.035   9.812  1.00 11.17           C
ATOM   1338  SG  CYS A 165      15.293  62.189   8.305  1.00 18.40           S
ATOM   1339  N   ALA A 166      13.356  64.969  10.216  1.00  9.90           N
ATOM   1340  CA  ALA A 166      13.475  66.394  10.046  1.00 10.42           C
ATOM   1341  C   ALA A 166      14.739  66.869  10.760  1.00 10.54           C
ATOM   1342  O   ALA A 166      15.224  66.284  11.739  1.00 11.08           O
ATOM   1343  CB  ALA A 166      12.255  67.104  10.634  1.00 11.37           C
ATOM   1344  N   GLN A 167      15.306  67.982  10.287  1.00 10.67           N
ATOM   1345  CA  GLN A 167      16.433  68.619  10.935  1.00 10.61           C
ATOM   1346  C   GLN A 167      15.999  69.985  11.425  1.00 12.37           C
ATOM   1347  O   GLN A 167      15.420  70.753  10.646  1.00 14.92           O
ATOM   1348  CB  GLN A 167      17.530  68.781   9.858  1.00 12.26           C
ATOM   1349  CG  GLN A 167      18.713  69.623  10.280  1.00 15.60           C
ATOM   1350  CD  GLN A 167      19.639  68.829  11.143  1.00 16.62           C
ATOM   1351  OE1 GLN A 167      20.257  67.884  10.684  1.00 17.28           O
ATOM   1352  NE2 GLN A 167      19.755  69.221  12.414  1.00 16.73           N
ATOM   1353  N   ILE A 168      16.219  70.249  12.708  1.00 12.92           N
ATOM   1354  CA  ILE A 168      16.024  71.589  13.227  1.00 13.79           C
ATOM   1355  C   ILE A 168      17.375  72.263  13.355  1.00 16.40           C
ATOM   1356  O   ILE A 168      18.438  71.614  13.445  1.00 15.31           O
ATOM   1357  CB  ILE A 168      15.209  71.585  14.532  1.00 13.24           C
ATOM   1358  CG1 ILE A 168      15.791  70.618  15.546  1.00 14.21           C
ATOM   1359  CD1 ILE A 168      15.077  70.736  16.948  1.00 17.92           C
ATOM   1360  CG2 ILE A 168      13.697  71.218  14.214  1.00 13.15           C
ATOM   1361  N   SER A 169      17.327  73.586  13.370  1.00 18.92           N
ATOM   1362  CA  SER A 169      18.548  74.385  13.425  1.00 22.30           C
ATOM   1363  C   SER A 169      18.246  75.682  14.139  1.00 23.37           C
ATOM   1364  O   SER A 169      17.103  75.970  14.467  1.00 20.18           O
ATOM   1365  CB  SER A 169      19.014  74.719  12.004  1.00 22.79           C
ATOM   1366  OG  SER A 169      18.036  75.434  11.277  1.00 26.18           O
ATOM   1367  N   LYS A 170      19.273  76.504  14.325  1.00 27.15           N
ATOM   1368  CA  LYS A 170      19.067  77.843  14.872  1.00 28.37           C
ATOM   1369  C   LYS A 170      18.067  78.643  14.063  1.00 27.91           C
ATOM   1370  O   LYS A 170      17.196  79.304  14.624  1.00 30.83           O
ATOM   1371  CB  LYS A 170      20.426  78.586  14.946  1.00 30.13           C
ATOM   1372  N   ASP A 171      18.186  78.570  12.750  1.00 29.61           N
ATOM   1373  CA  ASP A 171      17.294  79.248  11.824  1.00 29.87           C
ATOM   1374  C   ASP A 171      15.867  78.703  11.844  1.00 29.80           C
ATOM   1375  O   ASP A 171      14.921  79.481  11.725  1.00 31.39           O
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FIGURE 4W

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ATOM   1376  CB  ASP A 171      17.843  79.106  10.402  1.00 31.35           C
ATOM   1377  N   VAL A 172      15.714  77.369  11.925  1.00 26.96           N
ATOM   1378  CA  VAL A 172      14.390  76.723  11.880  1.00 24.06           C
ATOM   1379  C   VAL A 172      14.296  75.794  13.083  1.00 20.12           C
ATOM   1380  O   VAL A 172      14.585  74.593  12.984  1.00 17.74           O
ATOM   1381  CB  VAL A 172      14.154  75.913  10.566  1.00 25.93           C
ATOM   1382  CG1 VAL A 172      12.640  75.460  10.458  1.00 25.55           C
ATOM   1383  CG2 VAL A 172      14.515  76.750   9.362  1.00 29.52           C
ATOM   1384  N   PRO A 173      14.066  76.362  14.261  1.00 18.09           N
ATOM   1385  CA  PRO A 173      14.181  75.598  15.493  1.00 17.54           C
ATOM   1386  C   PRO A 173      12.990  74.665  15.758  1.00 14.47           C
ATOM   1387  O   PRO A 173      13.180  73.829  16.605  1.00 15.92           O
ATOM   1388  CB  PRO A 173      14.269  76.675  16.579  1.00 19.22           C
ATOM   1389  CG  PRO A 173      13.518  77.888  15.942  1.00 19.62           C
ATOM   1390  CD  PRO A 173      13.759  77.796  14.497  1.00 19.89           C
ATOM   1391  N   LYS A 174      11.867  74.817  15.058  1.00 14.35           N
ATOM   1392  CA  LYS A 174      10.699  73.955  15.280  1.00 12.12           C
ATOM   1393  C   LYS A 174      10.114  73.498  13.968  1.00 12.33           C
ATOM   1394  O   LYS A 174      10.252  74.167  12.915  1.00 12.75           O
ATOM   1395  CB  LYS A 174       9.563  74.712  15.999  1.00 13.82           C
ATOM   1396  CG  LYS A 174       9.946  75.391  17.333  1.00 17.26           C
ATOM   1397  CD  LYS A 174      10.276  74.464  18.416  1.00 20.49           C
ATOM   1398  CE  LYS A 174      10.242  75.226  19.782  1.00 25.33           C
ATOM   1399  NZ  LYS A 174      11.027  74.503  20.812  1.00 26.71           N
ATOM   1400  N   ARG A 175       9.402  72.384  14.024  1.00  9.90           N
ATOM   1401  CA  ARG A 175       8.638  71.866  12.897  1.00 10.64           C
ATOM   1402  C   ARG A 175       7.155  71.976  13.173  1.00 10.65           C
ATOM   1403  O   ARG A 175       6.773  72.127  14.331  1.00 11.69           O
ATOM   1404  CB  ARG A 175       8.963  70.374  12.637  1.00 12.01           C
ATOM   1405  CG  ARG A 175      10.428  70.150  12.432  1.00 13.49           C
ATOM   1406  CD  ARG A 175      10.997  71.052  11.387  1.00 15.35           C
ATOM   1407  NE  ARG A 175      10.506  70.619  10.116  1.00 17.56           N
ATOM   1408  CZ  ARG A 175      11.334  70.479   9.083  1.00 25.77           C
ATOM   1409  NH1 ARG A 175      12.632  70.792   9.219  1.00 22.31           N
ATOM   1410  NH2 ARG A 175      10.877  70.023   7.920  1.00 28.34           N
ATOM   1411  N   LYS A 176       6.310  71.884  12.169  1.00 12.76           N
ATOM   1412  CA  LYS A 176       4.858  71.816  12.468  1.00 13.73           C
ATOM   1413  C   LYS A 176       4.065  70.870  11.598  1.00 13.58           C
ATOM   1414  O   LYS A 176       2.856  70.857  11.655  1.00 15.23           O
ATOM   1415  CB  LYS A 176       4.243  73.225  12.501  1.00 16.85           C
ATOM   1416  CG  LYS A 176       4.644  74.081  11.285  1.00 18.27           C
ATOM   1417  CD  LYS A 176       3.863  73.661  10.072  1.00 20.51           C
ATOM   1418  CE  LYS A 176       3.809  74.737   8.964  1.00 26.84           C
ATOM   1419  NZ  LYS A 176       5.183  75.121   8.479  1.00 28.43           N
HETATM 1420  N   SEP A 177       4.768  70.055  10.829  1.00 13.46           N
HETATM 1421  CA  SEP A 177       4.093  69.134   9.911  1.00 12.36           C
HETATM 1422  C   SEP A 177       3.394  68.000  10.637  1.00 10.53           C
HETATM 1423  O   SEP A 177       3.900  67.449  11.622  1.00 12.66           O
HETATM 1424  CB  SEP A 177       5.133  68.493   8.981  1.00 12.77           C
HETATM 1425  OG  SEP A 177       5.777  69.492   8.215  1.00 14.27           O
HETATM 1426  P   SEP A 177       7.356  69.618   8.231  1.00 14.99           P
HETATM 1427  O1P SEP A 177       7.859  69.822   9.699  1.00 17.47           O
HETATM 1428  O2P SEP A 177       7.643  70.963   7.445  1.00 17.05           O
HETATM 1429  O3P SEP A 177       7.935  68.362   7.575  1.00 17.97           O
ATOM   1430  N   LEU A 178       2.202  67.631  10.130  1.00 12.36           N
ATOM   1431  CA  LEU A 178       1.495  66.482  10.676  1.00 14.50           C
ATOM   1432  C   LEU A 178       2.041  65.211  10.012  1.00 13.90           C
ATOM   1433  O   LEU A 178       1.641  64.851   8.867  1.00 16.12           O
ATOM   1434  CB  LEU A 178      -0.018  66.630  10.306  1.00 17.41           C
ATOM   1435  CG  LEU A 178      -0.809  65.417  10.783  1.00 20.12           C
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FIGURE 4X

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ATOM   1436  CD1 LEU A 178      -1.316  65.733  12.099  1.00 20.93           C
ATOM   1437  CD2 LEU A 178      -2.009  65.146   9.821  1.00 30.24           C
ATOM   1438  N   VAL A 179       2.947  64.536  10.682  1.00 13.68           N
ATOM   1439  CA  VAL A 179       3.626  63.371  10.107  1.00 14.09           C
ATOM   1440  C   VAL A 179       3.719  62.319  11.185  1.00 13.92           C
ATOM   1441  O   VAL A 179       3.763  62.617  12.406  1.00 15.95           O
ATOM   1442  CB  VAL A 179       5.072  63.680   9.576  1.00 14.27           C
ATOM   1443  CG1 VAL A 179       5.002  64.657   8.365  1.00 17.80           C
ATOM   1444  CG2 VAL A 179       5.918  64.247  10.641  1.00 20.28           C
ATOM   1445  N   GLY A 180       3.798  61.108  10.751  1.00 13.90           N
ATOM   1446  CA  GLY A 180       4.037  59.989  11.656  1.00 13.36           C
ATOM   1447  C   GLY A 180       2.948  58.972  11.417  1.00 12.77           C
ATOM   1448  O   GLY A 180       2.307  58.979  10.372  1.00 16.01           O
ATOM   1449  N   THR A 181       2.751  58.106  12.366  1.00 10.12           N
ATOM   1450  CA  THR A 181       1.726  57.057  12.259  1.00 10.40           C
ATOM   1451  C   THR A 181       0.710  57.328  13.371  1.00 12.80           C
ATOM   1452  O   THR A 181       1.116  57.466  14.533  1.00 12.95           O
ATOM   1453  CB  THR A 181       2.415  55.700  12.430  1.00 13.12           C
ATOM   1454  OG1 THR A 181       3.451  55.559  11.424  1.00 14.51           O
ATOM   1455  CG2 THR A 181       1.406  54.555  12.136  1.00 15.33           C
ATOM   1456  N   PRO A 182      -0.579  57.373  13.066  1.00 12.66           N
ATOM   1457  CA  PRO A 182      -1.625  57.908  13.983  1.00 12.21           C
ATOM   1458  C   PRO A 182      -1.511  57.516  15.470  1.00 11.56           C
ATOM   1459  O   PRO A 182      -1.463  58.447  16.339  1.00 13.00           O
ATOM   1460  CB  PRO A 182      -2.915  57.372  13.373  1.00 14.40           C
ATOM   1461  CG  PRO A 182      -2.630  57.402  11.925  1.00 16.21           C
ATOM   1462  CD  PRO A 182      -1.151  57.026  11.745  1.00 13.73           C
ATOM   1463  N   TYR A 183      -1.383  56.222  15.780  1.00 10.05           N
ATOM   1464  CA  TYR A 183      -1.501  55.776  17.159  1.00  8.90           C
ATOM   1465  C   TYR A 183      -0.267  56.140  17.986  1.00  8.87           C
ATOM   1466  O   TYR A 183      -0.298  56.072  19.224  1.00 10.15           O
ATOM   1467  CB  TYR A 183      -1.670  54.225  17.172  1.00  8.81           C
ATOM   1468  CG  TYR A 183      -2.869  53.781  16.382  1.00 10.55           C
ATOM   1469  CD1 TYR A 183      -2.756  53.443  15.049  1.00  9.81           C
ATOM   1470  CE1 TYR A 183      -3.889  53.035  14.322  1.00 12.57           C
ATOM   1471  CZ  TYR A 183      -5.121  53.009  14.941  1.00 12.40           C
ATOM   1472  OH  TYR A 183      -6.246  52.622  14.191  1.00 15.63           O
ATOM   1473  CE2 TYR A 183      -5.281  53.373  16.262  1.00 12.08           C
ATOM   1474  CD2 TYR A 183      -4.113  53.756  16.996  1.00 11.93           C
ATOM   1475  N   TRP A 184       0.837  56.458  17.275  1.00  6.24           N
ATOM   1476  CA  TRP A 184       2.090  56.829  17.956  1.00  7.39           C
ATOM   1477  C   TRP A 184       2.392  58.347  17.950  1.00  8.67           C
ATOM   1478  O   TRP A 184       3.374  58.779  18.568  1.00  9.65           O
ATOM   1479  CB  TRP A 184       3.280  56.128  17.264  1.00  8.46           C
ATOM   1480  CG  TRP A 184       3.297  54.633  17.534  1.00  7.98           C
ATOM   1481  CD1 TRP A 184       4.030  53.964  18.462  1.00  8.38           C
ATOM   1482  NE1 TRP A 184       3.783  52.608  18.370  1.00  9.41           N
ATOM   1483  CE2 TRP A 184       2.864  52.399  17.373  1.00  9.50           C
ATOM   1484  CD2 TRP A 184       2.553  53.641  16.816  1.00  8.81           C
ATOM   1485  CE3 TRP A 184       1.676  53.709  15.739  1.00  9.62           C
ATOM   1486  CZ3 TRP A 184       1.093  52.535  15.237  1.00 10.59           C
ATOM   1487  CH2 TRP A 184       1.415  51.298  15.830  1.00 11.10           C
ATOM   1488  CZ2 TRP A 184       2.304  51.191  16.876  1.00 11.66           C
ATOM   1489  N   MET A 185       1.526  59.136  17.329  1.00  8.01           N
ATOM   1490  CA  MET A 185       1.810  60.579  17.174  1.00  9.95           C
ATOM   1491  C   MET A 185       1.625  61.344  18.464  1.00  8.30           C
ATOM   1492  O   MET A 185       0.613  61.182  19.166  1.00 10.11           O
ATOM   1493  CB  MET A 185       0.876  61.175  16.152  1.00 12.15           C
ATOM   1494  CG BMET A 185       0.943  60.409  14.831  0.35 11.68           C
ATOM   1495  CG AMET A 185       1.268  61.002  14.785  0.65 15.46           C
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FIGURE 4Y

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ATOM   1496  SD BMET A 185      -0.032  61.134  13.466  0.35 20.34           S
ATOM   1497  SD AMET A 185      -0.256  61.705  13.867  0.65 22.73           S
ATOM   1498  CE BMET A 185       0.204  62.883  13.794  0.35  9.05           C
ATOM   1499  CE AMET A 185       0.294  61.114  12.365  0.65 16.07           C
ATOM   1500  N   ALA A 186       2.557  62.255  18.761  1.00  8.40           N
ATOM   1501  CA  ALA A 186       2.414  63.079  19.952  1.00  9.30           C
ATOM   1502  C   ALA A 186       1.256  64.078  19.779  1.00  8.17           C
ATOM   1503  O   ALA A 186       0.947  64.544  18.682  1.00  7.35           O
ATOM   1504  CB  ALA A 186       3.675  63.863  20.148  1.00  9.31           C
ATOM   1505  N   PRO A 187       0.592  64.484  20.874  1.00  8.10           N
ATOM   1506  CA  PRO A 187      -0.588  65.349  20.726  1.00  9.54           C
ATOM   1507  C   PRO A 187      -0.241  66.680  20.041  1.00  9.25           C
ATOM   1508  O   PRO A 187      -1.086  67.179  19.304  1.00 10.75           O
ATOM   1509  CB  PRO A 187      -1.026  65.620  22.167  1.00 11.10           C
ATOM   1510  CG  PRO A 187      -0.536  64.371  22.945  1.00 13.94           C
ATOM   1511  CD  PRO A 187       0.807  64.072  22.272  1.00  9.31           C
ATOM   1512  N   GLU A 188       0.941  67.211  20.293  1.00  9.24           N
ATOM   1513  CA  GLU A 188       1.294  68.506  19.641  1.00 10.61           C
ATOM   1514  C   GLU A 188       1.477  68.341  18.130  1.00 12.25           C
ATOM   1515  O   GLU A 188       1.294  69.293  17.375  1.00 12.90           O
ATOM   1516  CB  GLU A 188       2.555  69.132  20.286  1.00 13.06           C
ATOM   1517  CG  GLU A 188       3.839  68.304  20.205  1.00 12.22           C
ATOM   1518  CD  GLU A 188       4.096  67.358  21.408  1.00 11.62           C
ATOM   1519  OE1 GLU A 188       5.290  67.177  21.681  1.00 11.54           O
ATOM   1520  OE2 GLU A 188       3.121  66.834  22.072  1.00 11.85           O
ATOM   1521  N   VAL A 189       1.825  67.120  17.669  1.00  8.86           N
ATOM   1522  CA  VAL A 189       1.903  66.886  16.224  1.00 10.55           C
ATOM   1523  C   VAL A 189       0.486  66.872  15.669  1.00 11.89           C
ATOM   1524  O   VAL A 189       0.210  67.508  14.636  1.00 10.78           O
ATOM   1525  CB  VAL A 189       2.631  65.575  15.914  1.00 11.02           C
ATOM   1526  CG1 VAL A 189       2.590  65.316  14.340  1.00 10.85           C
ATOM   1527  CG2 VAL A 189       4.039  65.571  16.454  1.00  9.84           C
ATOM   1528  N   ILE A 190      -0.437  66.146  16.335  1.00  9.02           N
ATOM   1529  CA  ILE A 190      -1.785  66.062  15.839  1.00 10.82           C
ATOM   1530  C   ILE A 190      -2.406  67.463  15.753  1.00 11.52           C
ATOM   1531  O   ILE A 190      -3.169  67.757  14.795  1.00 14.37           O
ATOM   1532  CB  ILE A 190      -2.612  65.121  16.733  1.00 10.77           C
ATOM   1533  CG1 ILE A 190      -1.925  63.760  16.715  1.00 11.16           C
ATOM   1534  CD1 ILE A 190      -2.444  62.833  17.822  1.00 11.16           C
ATOM   1535  CG2 ILE A 190      -4.034  65.015  16.202  1.00 11.05           C
ATOM   1536  N   SER A 191      -2.108  68.304  16.740  1.00 12.67           N
ATOM   1537  CA  SER A 191      -2.681  69.658  16.733  1.00 14.48           C
ATOM   1538  C   SER A 191      -1.900  70.618  15.827  1.00 14.97           C
ATOM   1539  O   SER A 191      -2.289  71.807  15.758  1.00 18.65           O
ATOM   1540  CB BSER A 191      -2.690  70.248  18.169  0.35 14.86           C
ATOM   1541  CB ASER A 191      -2.783  70.227  18.133  0.65 14.93           C
ATOM   1542  OG BSER A 191      -2.999  69.321  19.224  0.35 16.01           O
ATOM   1543  OG ASER A 191      -1.509  70.338  18.716  0.65 13.70           O
ATOM   1544  N   ARG A 192      -0.875  70.140  15.106  1.00 14.86           N
ATOM   1545  CA  ARG A 192       0.000  70.970  14.240  1.00 15.75           C
ATOM   1546  C   ARG A 192       0.554  72.209  14.987  1.00 15.23           C
ATOM   1547  O   ARG A 192       0.705  73.299  14.404  1.00 16.66           O
ATOM   1548  CB  ARG A 192      -0.617  71.374  12.885  1.00 17.48           C
ATOM   1549  CG  ARG A 192      -1.253  70.199  12.020  1.00 19.20           C
ATOM   1550  CD  ARG A 192      -2.165  70.773  10.953  1.00 25.95           C
ATOM   1551  NE  ARG A 192      -2.832  69.726  10.172  1.00 30.81           N
ATOM   1552  CZ  ARG A 192      -2.295  69.195   9.093  1.00 33.77           C
ATOM   1553  NH1 ARG A 192      -1.100  69.625   8.692  1.00 33.90           N
ATOM   1554  NH2 ARG A 192      -2.937  68.246   8.413  1.00 32.60           N
ATOM   1555  N   SER A 193       0.908  72.011  16.253  1.00 12.70           N
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FIGURE 4Z

ATOM	1556	CA	SER	A	193	1.608	73.060	17.010	1.00	11.95	C
ATOM	1557	C	SER	A	193	3.058	73.031	16.577	1.00	13.55	C
ATOM	1558	O	SER	A	193	3.546	71.964	16.073	1.00	15.54	O
ATOM	1559	CB	SER	A	193	1.546	72.726	18.499	1.00	12.38	C
ATOM	1560	OG	SER	A	193	0.166	72.811	18.882	1.00	17.59	O
ATOM	1561	N	LEU	A	194	3.808	74.090	16.843	1.00	10.60	N
ATOM	1562	CA	LEU	A	194	5.254	73.999	16.649	1.00	10.41	C
ATOM	1563	C	LEU	A	194	5.852	73.017	17.662	1.00	10.82	C
ATOM	1564	O	LEU	A	194	5.482	73.033	18.878	1.00	12.22	O
ATOM	1565	CB	LEU	A	194	5.891	75.399	16.885	1.00	12.36	C
ATOM	1566	CG	LEU	A	194	5.549	76.410	15.816	1.00	14.42	C
ATOM	1567	CD1	LEU	A	194	6.088	77.737	16.355	1.00	20.14	C
ATOM	1568	CD2	LEU	A	194	6.165	76.005	14.521	1.00	19.06	C
ATOM	1569	N	TYR	A	195	6.754	72.137	17.186	1.00	8.49	N
ATOM	1570	CA	TYR	A	195	7.335	71.127	18.066	1.00	8.06	C
ATOM	1571	C	TYR	A	195	8.789	70.865	17.686	1.00	9.49	C
ATOM	1572	O	TYR	A	195	9.226	71.219	16.604	1.00	9.62	O
ATOM	1573	CB	TYR	A	195	6.496	69.851	17.954	1.00	9.99	C
ATOM	1574	CG	TYR	A	195	6.439	69.226	16.575	1.00	8.56	C
ATOM	1575	CD1	TYR	A	195	7.506	68.446	16.117	1.00	8.82	C
ATOM	1576	CE1	TYR	A	195	7.478	67.846	14.864	1.00	8.39	C
ATOM	1577	CZ	TYR	A	195	6.349	67.973	14.098	1.00	9.22	C
ATOM	1578	OH	TYR	A	195	6.286	67.441	12.830	1.00	10.36	O
ATOM	1579	CE2	TYR	A	195	5.252	68.741	14.516	1.00	8.80	C
ATOM	1580	CD2	TYR	A	195	5.305	69.365	15.781	1.00	9.46	C
ATOM	1581	N	ALA	A	196	9.467	70.118	18.540	1.00	8.73	N
ATOM	1582	CA	ALA	A	196	10.877	69.779	18.282	1.00	10.77	C
ATOM	1583	C	ALA	A	196	11.087	68.305	18.697	1.00	10.06	C
ATOM	1584	O	ALA	A	196	10.212	67.437	18.471	1.00	9.50	O
ATOM	1585	CB	ALA	A	196	11.773	70.773	19.041	1.00	12.36	C
ATOM	1586	N	THR	A	197	12.222	67.986	19.283	1.00	8.93	N
ATOM	1587	CA	THR	A	197	12.563	66.559	19.470	1.00	9.00	C
ATOM	1588	C	THR	A	197	11.676	65.809	20.467	1.00	10.46	C
ATOM	1589	O	THR	A	197	11.662	64.564	20.484	1.00	10.59	O
ATOM	1590	CB	THR	A	197	14.028	66.418	19.925	1.00	9.46	C
ATOM	1591	OG1	THR	A	197	14.237	67.188	21.117	1.00	12.69	O
ATOM	1592	CG2	THR	A	197	15.023	66.986	18.862	1.00	8.91	C
ATOM	1593	N	GLU	A	198	10.938	66.562	21.293	1.00	7.99	N
ATOM	1594	CA	GLU	A	198	10.162	65.885	22.341	1.00	9.91	C
ATOM	1595	C	GLU	A	198	9.140	64.912	21.786	1.00	8.33	C
ATOM	1596	O	GLU	A	198	8.685	64.011	22.487	1.00	9.01	O
ATOM	1597	CB	GLU	A	198	9.350	66.930	23.163	1.00	12.21	C
ATOM	1598	CG	GLU	A	198	10.221	68.109	23.583	1.00	15.73	C
ATOM	1599	CD	GLU	A	198	10.301	69.287	22.577	1.00	23.04	C
ATOM	1600	OE1	GLU	A	198	9.772	69.231	21.453	1.00	17.65	O
ATOM	1601	OE2	GLU	A	198	10.849	70.356	22.938	1.00	29.80	O
ATOM	1602	N	VAL	A	199	8.750	65.113	20.525	1.00	7.21	N
ATOM	1603	CA	VAL	A	199	7.724	64.256	19.938	1.00	7.54	C
ATOM	1604	C	VAL	A	199	8.153	62.799	19.863	1.00	7.89	C
ATOM	1605	O	VAL	A	199	7.307	61.877	20.006	1.00	8.50	O
ATOM	1606	CB	VAL	A	199	7.235	64.739	18.557	1.00	9.96	C
ATOM	1607	CG1	VAL	A	199	6.752	66.173	18.685	1.00	9.62	C
ATOM	1608	CG2	VAL	A	199	8.312	64.649	17.497	1.00	9.29	C
ATOM	1609	N	ASP	A	200	9.449	62.555	19.707	1.00	6.38	N
ATOM	1610	CA	ASP	A	200	9.949	61.159	19.594	1.00	7.47	C
ATOM	1611	C	ASP	A	200	9.851	60.431	20.944	1.00	7.82	C
ATOM	1612	O	ASP	A	200	9.719	59.207	21.004	1.00	8.32	O
ATOM	1613	CB	ASP	A	200	11.422	61.185	19.158	1.00	7.45	C
ATOM	1614	CG	ASP	A	200	11.605	61.427	17.703	1.00	10.61	C
ATOM	1615	OD1	ASP	A	200	10.683	61.256	16.896	1.00	8.39	O

FIGURE 4AA

ATOM	1616	OD2	ASP	A	200	12.750	61.788	17.354	1.00	10.13	O
ATOM	1617	N	ILE	A	201	9.935	61.225	22.044	1.00	7.20	N
ATOM	1618	CA	ILE	A	201	9.844	60.594	23.379	1.00	7.27	C
ATOM	1619	C	ILE	A	201	8.417	60.163	23.660	1.00	7.11	C
ATOM	1620	O	ILE	A	201	8.220	59.096	24.264	1.00	8.53	O
ATOM	1621	CB	ILE	A	201	10.336	61.598	24.456	1.00	7.31	C
ATOM	1622	CG1	ILE	A	201	11.757	62.067	24.129	1.00	8.54	C
ATOM	1623	CD1	ILE	A	201	12.827	60.966	24.008	1.00	11.46	C
ATOM	1624	CG2	ILE	A	201	10.172	60.962	25.893	1.00	8.88	C
ATOM	1625	N	TRP	A	202	7.425	60.951	23.264	1.00	6.93	N
ATOM	1626	CA	TRP	A	202	6.076	60.466	23.359	1.00	7.32	C
ATOM	1627	C	TRP	A	202	5.890	59.195	22.558	1.00	7.61	C
ATOM	1628	O	TRP	A	202	5.305	58.225	23.065	1.00	7.77	O
ATOM	1629	CB	TRP	A	202	5.079	61.500	22.864	1.00	6.52	C
ATOM	1630	CG	TRP	A	202	3.658	61.070	22.870	1.00	5.59	C
ATOM	1631	CD1	TRP	A	202	3.056	60.258	21.933	1.00	6.84	C
ATOM	1632	NE1	TRP	A	202	1.729	60.066	22.257	1.00	7.09	N
ATOM	1633	CE2	TRP	A	202	1.447	60.732	23.434	1.00	6.34	C
ATOM	1634	CD2	TRP	A	202	2.656	61.366	23.850	1.00	6.26	C
ATOM	1635	CE3	TRP	A	202	2.654	62.133	25.026	1.00	7.25	C
ATOM	1636	CZ3	TRP	A	202	1.450	62.229	25.762	1.00	8.08	C
ATOM	1637	CH2	TRP	A	202	0.267	61.593	25.320	1.00	9.21	C
ATOM	1638	CZ2	TRP	A	202	0.250	60.828	24.161	1.00	8.26	C
ATOM	1639	N	SER	A	203	6.281	59.200	21.283	1.00	7.30	N
ATOM	1640	CA	SER	A	203	6.160	57.946	20.492	1.00	7.28	C
ATOM	1641	C	SER	A	203	6.842	56.739	21.159	1.00	7.85	C
ATOM	1642	O	SER	A	203	6.330	55.613	21.081	1.00	9.09	O
ATOM	1643	CB	SER	A	203	6.714	58.168	19.053	1.00	7.37	C
ATOM	1644	OG	SER	A	203	6.056	59.282	18.408	1.00	9.64	O
ATOM	1645	N	LEU	A	204	8.052	56.946	21.730	1.00	7.96	N
ATOM	1646	CA	LEU	A	204	8.717	55.891	22.493	1.00	8.23	C
ATOM	1647	C	LEU	A	204	7.842	55.396	23.629	1.00	8.98	C
ATOM	1648	O	LEU	A	204	7.795	54.201	23.849	1.00	8.44	O
ATOM	1649	CB	LEU	A	204	10.068	56.373	22.999	1.00	9.47	C
ATOM	1650	CG	LEU	A	204	10.816	55.346	23.843	1.00	13.16	C
ATOM	1651	CD1	LEU	A	204	11.183	54.166	22.978	1.00	17.38	C
ATOM	1652	CD2	LEU	A	204	12.094	56.037	24.311	1.00	15.16	C
ATOM	1653	N	GLY	A	205	7.174	56.329	24.321	1.00	7.32	N
ATOM	1654	CA	GLY	A	205	6.216	55.982	25.391	1.00	8.11	C
ATOM	1655	C	GLY	A	205	5.180	55.032	24.856	1.00	7.63	C
ATOM	1656	O	GLY	A	205	4.814	54.017	25.506	1.00	8.35	O
ATOM	1657	N	ILE	A	206	4.629	55.363	23.684	1.00	7.27	N
ATOM	1658	CA	ILE	A	206	3.592	54.496	23.125	1.00	7.01	C
ATOM	1659	C	ILE	A	206	4.196	53.128	22.743	1.00	9.17	C
ATOM	1660	O	ILE	A	206	3.529	52.093	22.908	1.00	9.38	O
ATOM	1661	CB	ILE	A	206	2.953	55.213	21.878	1.00	7.93	C
ATOM	1662	CG1	ILE	A	206	2.306	56.571	22.249	1.00	7.47	C
ATOM	1663	CD1	ILE	A	206	1.066	56.395	23.228	1.00	9.57	C
ATOM	1664	CG2	ILE	A	206	1.925	54.272	21.184	1.00	7.57	C
ATOM	1665	N	MET	A	207	5.441	53.111	22.250	1.00	9.43	N
ATOM	1666	CA	MET	A	207	6.096	51.837	22.012	1.00	9.82	C
ATOM	1667	C	MET	A	207	6.273	51.016	23.327	1.00	10.15	C
ATOM	1668	O	MET	A	207	6.208	49.786	23.291	1.00	11.22	O
ATOM	1669	CB	MET	A	207	7.480	52.052	21.331	1.00	11.50	C
ATOM	1670	CG	MET	A	207	7.916	50.733	20.640	1.00	14.03	C
ATOM	1671	SD	MET	A	207	9.430	51.012	19.685	1.00	20.41	S
ATOM	1672	CE	MET	A	207	10.638	50.841	21.038	1.00	21.65	C
ATOM	1673	N	VAL	A	208	6.568	51.677	24.459	1.00	8.04	N
ATOM	1674	CA	VAL	A	208	6.652	50.946	25.724	1.00	9.84	C
ATOM	1675	C	VAL	A	208	5.292	50.318	26.075	1.00	10.44	C

FIGURE 4BB

```
ATOM   1676  O   VAL A 208       5.201  49.148  26.50
ATOM   1677  CB  VAL A 208       7.176  51.854  26.87
ATOM   1678  CG1 VAL A 208       7.049  51.124  28.26
ATOM   1679  CG2 VAL A 208       8.673  52.293  26.55
ATOM   1680  N   ILE A 209       4.242  51.047  25.79
ATOM   1681  CA  ILE A 209       2.884  50.469  25.94
ATOM   1682  C   ILE A 209       2.724  49.248  25.02
ATOM   1683  O   ILE A 209       2.197  48.203  25.44
ATOM   1684  CB  ILE A 209       1.758  51.511  25.73
ATOM   1685  CG1 ILE A 209       1.837  52.557  26.87
ATOM   1686  CD1 ILE A 209       0.700  53.644  26.79
ATOM   1687  CG2 ILE A 209       0.359  50.839  25.70
ATOM   1688  N   GLU A 210       3.182  49.332  23.78
ATOM   1689  CA  GLU A 210       3.134  48.140  22.90
ATOM   1690  C   GLU A 210       3.873  46.986  23.61
ATOM   1691  O   GLU A 210       3.386  45.849  23.54
ATOM   1692  CB  GLU A 210       3.859  48.338  21.53
ATOM   1693  CG  GLU A 210       3.315  49.377  20.59
ATOM   1694  CD  GLU A 210       4.099  49.329  19.26
ATOM   1695  OE1 GLU A 210       4.948  50.187  18.99
ATOM   1696  OE2 GLU A 210       3.983  48.338  18.49
ATOM   1697  N   MET A 211       5.054  47.222  24.18
ATOM   1698  CA  MET A 211       5.833  46.124  24.83
ATOM   1699  C   MET A 211       5.153  45.538  26.05
ATOM   1700  O   MET A 211       5.217  44.313  26.26
ATOM   1701  CB  MET A 211       7.260  46.559  25.14
ATOM   1702  CG  MET A 211       8.028  46.807  23.84
ATOM   1703  SD  MET A 211       9.789  47.110  24.10
ATOM   1704  CE  MET A 211       9.830  48.653  24.72
ATOM   1705  N   VAL A 212       4.458  46.380  26.85
ATOM   1706  CA  VAL A 212       3.802  45.870  28.07
ATOM   1707  C   VAL A 212       2.435  45.261  27.80
ATOM   1708  O   VAL A 212       2.124  44.192  28.34
ATOM   1709  CB  VAL A 212       3.682  46.981  29.08
ATOM   1710  CG1 VAL A 212       2.849  46.514  30.35
ATOM   1711  CG2 VAL A 212       5.090  47.467  29.48
ATOM   1712  N   ASP A 213       1.606  45.939  26.98
ATOM   1713  CA  ASP A 213       0.200  45.520  26.72
ATOM   1714  C   ASP A 213       0.026  44.676  25.48
ATOM   1715  O   ASP A 213      -0.984  43.937  25.3
ATOM   1716  CB  ASP A 213      -0.684  46.743  26.55
ATOM   1717  CG  ASP A 213      -1.027  47.438  27.87
ATOM   1718  OD1 ASP A 213      -0.830  46.904  29.0
ATOM   1719  OD2 ASP A 213      -1.575  48.563  27.8
ATOM   1720  N   GLY A 214       0.897  44.845  24.4
ATOM   1721  CA  GLY A 214       0.766  44.089  23.2
ATOM   1722  C   GLY A 214       0.292  44.914  22.0
ATOM   1723  O   GLY A 214       0.261  44.439  20.9
ATOM   1724  N   GLU A 215      -0.147  46.139  22.3
ATOM   1725  CA  GLU A 215      -0.659  47.020  21.2
ATOM   1726  C   GLU A 215      -0.679  48.439  21.7
ATOM   1727  O   GLU A 215      -0.697  48.635  23.0
ATOM   1728  CB  GLU A 215      -2.080  46.651  20.8
ATOM   1729  CG  GLU A 215      -3.122  46.691  21.8
ATOM   1730  CD  GLU A 215      -4.533  46.304  21.3
ATOM   1731  OE1 GLU A 215      -4.641  45.655  20.2
ATOM   1732  OE2 GLU A 215      -5.553  46.701  21.9
ATOM   1733  N   PRO A 216      -0.681  49.447  20.9
ATOM   1734  CA  PRO A 216      -0.789  50.816  21.4
ATOM   1735  C   PRO A 216      -2.197  51.123  21.9
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FIGURE 4CC

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ATOM   1736  O   PRO A 216      -3.182  50.457  21.634  1.00 11.41           O
ATOM   1737  CB  PRO A 216      -0.544  51.723  20.253  1.00 12.59           C
ATOM   1738  CG  PRO A 216      -0.513  50.870  19.094  1.00 14.60           C
ATOM   1739  CD  PRO A 216      -0.539  49.406  19.479  1.00 12.29           C
ATOM   1740  N   PRO A 217      -2.337  52.233  22.658  1.00 10.60           N
ATOM   1741  CA  PRO A 217      -3.673  52.685  23.073  1.00 11.93           C
ATOM   1742  C   PRO A 217      -4.580  53.004  21.869  1.00 11.30           C
ATOM   1743  O   PRO A 217      -4.119  53.352  20.756  1.00 11.28           O
ATOM   1744  CB  PRO A 217      -3.390  54.022  23.837  1.00 13.60           C
ATOM   1745  CG  PRO A 217      -1.958  53.876  24.277  1.00 15.40           C
ATOM   1746  CD  PRO A 217      -1.231  53.114  23.141  1.00 10.48           C
ATOM   1747  N   TYR A 218      -5.894  52.796  22.055  1.00 11.15           N
ATOM   1748  CA  TYR A 218      -6.905  53.135  21.082  1.00 12.23           C
ATOM   1749  C   TYR A 218      -6.804  52.316  19.791  1.00 12.03           C
ATOM   1750  O   TYR A 218      -7.333  52.743  18.781  1.00 12.64           O
ATOM   1751  CB  TYR A 218      -6.822  54.624  20.732  1.00 13.61           C
ATOM   1752  CG  TYR A 218      -6.842  55.509  21.959  1.00 13.73           C
ATOM   1753  CD1 TYR A 218      -7.840  55.375  22.887  1.00 17.17           C
ATOM   1754  CE1 TYR A 218      -7.859  56.235  24.042  1.00 18.06           C
ATOM   1755  CZ  TYR A 218      -6.829  57.169  24.197  1.00 18.73           C
ATOM   1756  OH  TYR A 218      -6.801  58.024  25.274  1.00 20.43           O
ATOM   1757  CE2 TYR A 218      -5.840  57.304  23.270  1.00 15.71           C
ATOM   1758  CD2 TYR A 218      -5.835  56.434  22.173  1.00 14.33           C
ATOM   1759  N   PHE A 219      -6.181  51.146  19.861  1.00 11.61           N
ATOM   1760  CA  PHE A 219      -5.855  50.413  18.648  1.00 14.29           C
ATOM   1761  C   PHE A 219      -7.080  49.926  17.912  1.00 16.67           C
ATOM   1762  O   PHE A 219      -7.023  49.781  16.678  1.00 18.51           O
ATOM   1763  CB  PHE A 219      -4.897  49.234  18.940  1.00 14.89           C
ATOM   1764  CG  PHE A 219      -3.923  48.968  17.851  1.00 15.21           C
ATOM   1765  CD1 PHE A 219      -3.540  47.668  17.546  1.00 14.86           C
ATOM   1766  CE1 PHE A 219      -2.621  47.440  16.553  1.00 14.73           C
ATOM   1767  CZ  PHE A 219      -1.990  48.482  15.911  1.00 14.90           C
ATOM   1768  CE2 PHE A 219      -2.331  49.783  16.210  1.00 14.90           C
ATOM   1769  CD2 PHE A 219      -3.298  50.009  17.187  1.00 13.03           C
ATOM   1770  N   SER A 220      -8.178  49.712  18.620  1.00 19.72           N
ATOM   1771  CA  SER A 220      -9.410  49.245  17.961  1.00 22.26           C
ATOM   1772  C   SER A 220     -10.215  50.413  17.394  1.00 22.26           C
ATOM   1773  O   SER A 220     -11.208  50.210  16.683  1.00 23.48           O
ATOM   1774  CB  SER A 220     -10.273  48.407  18.915  1.00 24.24           C
ATOM   1775  OG  SER A 220     -10.626  49.183  20.064  1.00 27.24           O
ATOM   1776  N   ASP A 221      -9.811  51.647  17.691  1.00 17.37           N
ATOM   1777  CA  ASP A 221     -10.462  52.794  17.037  1.00 17.42           C
ATOM   1778  C   ASP A 221      -9.913  52.942  15.645  1.00 15.64           C
ATOM   1779  O   ASP A 221      -8.808  52.507  15.391  1.00 17.11           O
ATOM   1780  CB  ASP A 221     -10.194  54.096  17.813  1.00 17.42           C
ATOM   1781  CG  ASP A 221     -10.966  54.173  19.119  1.00 25.16           C
ATOM   1782  OD1 ASP A 221     -12.123  53.726  19.111  1.00 31.16           O
ATOM   1783  OD2 ASP A 221     -10.492  54.619  20.179  1.00 27.85           O
ATOM   1784  N   SER A 222     -10.678  53.536  14.737  1.00 14.70           N
ATOM   1785  CA  SER A 222     -10.139  53.953  13.424  1.00 15.25           C
ATOM   1786  C   SER A 222      -8.944  54.901  13.676  1.00 13.87           C
ATOM   1787  O   SER A 222      -8.849  55.534  14.728  1.00 13.38           O
ATOM   1788  CB  SER A 222     -11.216  54.622  12.586  1.00 16.93           C
ATOM   1789  OG  SER A 222     -11.267  56.040  12.861  1.00 22.00           O
ATOM   1790  N   PRO A 223      -8.015  54.974  12.734  1.00 12.63           N
ATOM   1791  CA  PRO A 223      -6.841  55.843  12.895  1.00 12.58           C
ATOM   1792  C   PRO A 223      -7.257  57.313  13.122  1.00 13.79           C
ATOM   1793  O   PRO A 223      -6.640  57.975  13.963  1.00 13.89           O
ATOM   1794  CB  PRO A 223      -6.106  55.684  11.566  1.00 14.54           C
ATOM   1795  CG  PRO A 223      -6.449  54.177  11.164  1.00 17.03           C
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FIGURE 4DD

```
ATOM   1796  CD  PRO A 223      -7.911  54.108  11.521  1.00 14.10           C
ATOM   1797  N   VAL A 224      -8.286  57.795  12.428  1.00 14.16           N
ATOM   1798  CA  VAL A 224      -8.719  59.185  12.580  1.00 16.18           C
ATOM   1799  C   VAL A 224      -9.381  59.409  13.962  1.00 15.57           C
ATOM   1800  O   VAL A 224      -9.080  60.397  14.658  1.00 15.46           O
ATOM   1801  CB  VAL A 224      -9.673  59.535  11.421  1.00 18.99           C
ATOM   1802  CG1 VAL A 224     -10.386  60.805  11.717  1.00 20.49           C
ATOM   1803  CG2 VAL A 224      -8.851  59.691  10.102  1.00 22.12           C
ATOM   1804  N   GLN A 225     -10.176  58.446  14.405  1.00 14.97           N
ATOM   1805  CA  GLN A 225     -10.731  58.528  15.747  1.00 14.39           C
ATOM   1806  C   GLN A 225      -9.634  58.444  16.830  1.00 13.92           C
ATOM   1807  O   GLN A 225      -9.678  59.193  17.856  1.00 14.67           O
ATOM   1808  CB BGLN A 225     -11.794  57.439  15.930  0.35 14.65           C
ATOM   1809  CB AGLN A 225     -11.799  57.430  15.970  0.65 16.87           C
ATOM   1810  CG BGLN A 225     -13.004  57.707  15.058  0.35 13.93           C
ATOM   1811  CG AGLN A 225     -12.231  57.269  17.424  0.65 21.48           C
ATOM   1812  CD AGLN A 225     -13.050  58.438  18.029  0.65 30.11           C
ATOM   1813  OE1AGLN A 225     -13.163  59.528  17.457  0.65 33.96           O
ATOM   1814  NE2AGLN A 225     -13.635  58.180  19.194  0.65 32.00           N
ATOM   1815  N   ALA A 226      -8.645  57.565  16.649  1.00 11.43           N
ATOM   1816  CA  ALA A 226      -7.581  57.450  17.649  1.00 12.14           C
ATOM   1817  C   ALA A 226      -6.872  58.822  17.785  1.00 10.16           C
ATOM   1818  O   ALA A 226      -6.521  59.248  18.893  1.00 11.83           O
ATOM   1819  CB  ALA A 226      -6.569  56.382  17.253  1.00 11.42           C
ATOM   1820  N   MET A 227      -6.606  59.457  16.652  1.00 11.14           N
ATOM   1821  CA  MET A 227      -5.918  60.768  16.662  1.00 11.08           C
ATOM   1822  C   MET A 227      -6.714  61.816  17.424  1.00 11.05           C
ATOM   1823  O   MET A 227      -6.107  62.626  18.140  1.00 11.22           O
ATOM   1824  CB  MET A 227      -5.625  61.267  15.256  1.00 11.85           C
ATOM   1825  CG BMET A 227      -4.493  60.477  14.633  0.35 13.17           C
ATOM   1826  CG AMET A 227      -4.452  60.514  14.682  0.65 15.25           C
ATOM   1827  SD BMET A 227      -4.307  60.675  12.850  0.35 14.48           S
ATOM   1828  SD AMET A 227      -3.872  61.220  13.132  0.65 19.84           S
ATOM   1829  CE BMET A 227      -3.913  62.430  12.732  0.35 13.01           C
ATOM   1830  CE AMET A 227      -5.273  60.839  12.126  0.65 16.60           C
ATOM   1831  N   LYS A 228      -8.026  61.789  17.261  1.00 11.40           N
ATOM   1832  CA  LYS A 228      -8.908  62.734  17.968  1.00 14.20           C
ATOM   1833  C   LYS A 228      -8.804  62.504  19.469  1.00 13.98           C
ATOM   1834  O   LYS A 228      -8.724  63.488  20.289  1.00 14.07           O
ATOM   1835  CB  LYS A 228     -10.356  62.534  17.547  1.00 15.01           C
ATOM   1836  CG  LYS A 228     -10.672  63.121  16.194  1.00 23.56           C
ATOM   1837  CD  LYS A 228     -12.169  62.928  15.932  1.00 31.05           C
ATOM   1838  CE  LYS A 228     -12.501  62.919  14.412  1.00 37.91           C
ATOM   1839  NZ  LYS A 228     -11.649  63.879  13.635  1.00 39.07           N
ATOM   1840  N   ARG A 229      -8.737  61.236  19.888  1.00 11.77           N
ATOM   1841  CA  ARG A 229      -8.620  60.969  21.312  1.00 12.30           C
ATOM   1842  C   ARG A 229      -7.267  61.389  21.840  1.00 12.27           C
ATOM   1843  O   ARG A 229      -7.155  62.000  22.916  1.00 12.33           O
ATOM   1844  CB  ARG A 229      -8.843  59.472  21.646  1.00 14.60           C
ATOM   1845  CG  ARG A 229     -10.256  59.046  21.239  1.00 20.61           C
ATOM   1846  CD  ARG A 229     -10.672  57.695  21.668  1.00 30.02           C
ATOM   1847  NE  ARG A 229     -10.840  57.579  23.113  1.00 35.51           N
ATOM   1848  CZ  ARG A 229     -11.268  56.455  23.693  1.00 39.66           C
ATOM   1849  NH1 ARG A 229     -11.374  56.378  25.006  1.00 39.35           N
ATOM   1850  NH2 ARG A 229     -11.566  55.395  22.941  1.00 39.25           N
ATOM   1851  N   LEU A 230      -6.223  61.073  21.074  1.00  9.56           N
ATOM   1852  CA  LEU A 230      -4.879  61.401  21.545  1.00 10.70           C
ATOM   1853  C   LEU A 230      -4.664  62.926  21.599  1.00 10.18           C
ATOM   1854  O   LEU A 230      -3.944  63.417  22.492  1.00 12.43           O
ATOM   1855  CB  LEU A 230      -3.818  60.854  20.584  1.00  9.90           C
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FIGURE 4EE

ATOM	1856	CG	LEU	A	230	-3.700	59.360	20.786	1.00	8.71	C
ATOM	1857	CD1	LEU	A	230	-3.115	58.664	19.468	1.00	13.82	C
ATOM	1858	CD2	LEU	A	230	-2.788	58.965	21.915	1.00	12.03	C
ATOM	1859	N	ARG	A	231	-5.259	63.647	20.654	1.00	11.94	N
ATOM	1860	CA	ARG	A	231	-5.050	65.088	20.521	1.00	13.39	C
ATOM	1861	C	ARG	A	231	-5.458	65.785	21.784	1.00	14.05	C
ATOM	1862	O	ARG	A	231	-4.724	66.643	22.260	1.00	18.09	O
ATOM	1863	CB	ARG	A	231	-5.868	65.630	19.348	1.00	13.53	C
ATOM	1864	CG	ARG	A	231	-5.621	67.141	18.964	1.00	16.48	C
ATOM	1865	CD	ARG	A	231	-6.780	67.672	18.143	1.00	16.02	C
ATOM	1866	NE	ARG	A	231	-6.457	68.999	17.556	1.00	22.48	N
ATOM	1867	CZ	ARG	A	231	-6.444	70.144	18.220	1.00	23.29	C
ATOM	1868	NH1	ARG	A	231	-6.718	70.187	19.510	1.00	23.31	N
ATOM	1869	NH2	ARG	A	231	-6.161	71.257	17.567	1.00	24.81	N
ATOM	1870	N	ASP	A	232	-6.580	65.387	22.341	1.00	14.93	N
ATOM	1871	CA	ASP	A	232	-7.097	66.167	23.487	1.00	17.99	C
ATOM	1872	C	ASP	A	232	-7.226	65.476	24.849	1.00	17.24	C
ATOM	1873	O	ASP	A	232	-7.595	66.126	25.817	1.00	16.11	O
ATOM	1874	CB	ASP	A	232	-8.414	66.819	23.135	1.00	21.42	C
ATOM	1875	CG	ASP	A	232	-8.325	67.742	21.890	1.00	25.74	C
ATOM	1876	OD1	ASP	A	232	-7.248	68.352	21.559	1.00	26.40	O
ATOM	1877	OD2	ASP	A	232	-9.349	67.913	21.190	1.00	31.42	O
ATOM	1878	N	SER	A	233	-6.905	64.203	24.949	1.00	12.98	N
ATOM	1879	CA	SER	A	233	-7.146	63.470	26.202	1.00	13.02	C
ATOM	1880	C	SER	A	233	-5.932	63.440	27.111	1.00	12.86	C
ATOM	1881	O	SER	A	233	-4.797	63.494	26.658	1.00	11.91	O
ATOM	1882	CB	SER	A	233	-7.605	62.017	25.899	1.00	14.97	C
ATOM	1883	OG	SER	A	233	-8.783	62.036	25.136	1.00	17.32	O
ATOM	1884	N	PRO	A	234	-6.097	63.262	28.420	1.00	11.22	N
ATOM	1885	CA	PRO	A	234	-4.949	62.968	29.284	1.00	12.07	C
ATOM	1886	C	PRO	A	234	-4.181	61.754	28.708	1.00	11.78	C
ATOM	1887	O	PRO	A	234	-4.794	60.941	27.999	1.00	13.26	O
ATOM	1888	CB	PRO	A	234	-5.582	62.614	30.632	1.00	13.85	C
ATOM	1889	CG	PRO	A	234	-6.858	63.382	30.580	1.00	14.18	C
ATOM	1890	CD	PRO	A	234	-7.379	63.296	29.171	1.00	14.29	C
ATOM	1891	N	PRO	A	235	-2.909	61.620	29.031	1.00	12.43	N
ATOM	1892	CA	PRO	A	235	-2.128	60.562	28.401	1.00	12.33	C
ATOM	1893	C	PRO	A	235	-2.685	59.179	28.693	1.00	13.90	C
ATOM	1894	O	PRO	A	235	-3.274	58.934	29.770	1.00	12.03	O
ATOM	1895	CB	PRO	A	235	-0.744	60.690	29.025	1.00	15.49	C
ATOM	1896	CG	PRO	A	235	-0.681	62.136	29.549	1.00	16.66	C
ATOM	1897	CD	PRO	A	235	-2.107	62.396	30.007	1.00	11.62	C
ATOM	1898	N	PRO	A	236	-2.485	58.266	27.751	1.00	12.06	N
ATOM	1899	CA	PRO	A	236	-3.067	56.940	27.894	1.00	14.02	C
ATOM	1900	C	PRO	A	236	-2.324	56.206	28.965	1.00	16.52	C
ATOM	1901	O	PRO	A	236	-1.143	56.431	29.196	1.00	17.17	O
ATOM	1902	CB	PRO	A	236	-2.815	56.305	26.510	1.00	13.82	C
ATOM	1903	CG	PRO	A	236	-1.650	57.081	25.922	1.00	15.95	C
ATOM	1904	CD	PRO	A	236	-1.748	58.464	26.490	1.00	13.01	C
ATOM	1905	N	LYS	A	237	-3.048	55.300	29.604	1.00	20.86	N
ATOM	1906	CA	LYS	A	237	-2.499	54.534	30.694	1.00	23.45	C
ATOM	1907	C	LYS	A	237	-2.296	53.081	30.257	1.00	23.21	C
ATOM	1908	O	LYS	A	237	-2.920	52.632	29.284	1.00	22.52	O
ATOM	1909	CB	LYS	A	237	-3.471	54.644	31.865	1.00	25.76	C
ATOM	1910	CG	LYS	A	237	-3.451	56.061	32.459	1.00	30.23	C
ATOM	1911	CD	LYS	A	237	-3.831	56.105	33.950	1.00	37.37	C
ATOM	1912	CE	LYS	A	237	-5.274	56.590	34.143	1.00	41.93	C
ATOM	1913	NZ	LYS	A	237	-5.652	57.721	33.209	1.00	45.39	N
ATOM	1914	N	LEU	A	238	-1.377	52.391	30.930	1.00	22.06	N
ATOM	1915	CA	LEU	A	238	-1.179	50.966	30.681	1.00	21.36	C

FIGURE 4FF

```
ATOM   1916  C   LEU A 238      -2.417  50.185  31.094  1.00 21.85           C
ATOM   1917  O   LEU A 238      -2.928  50.409  32.178  1.00 24.44           O
ATOM   1918  CB  LEU A 238      -0.072  50.434  31.576  1.00 21.93           C
ATOM   1919  CG  LEU A 238       1.347  50.798  31.203  1.00 24.88           C
ATOM   1920  CD1 LEU A 238       2.248  50.357  32.356  1.00 24.48           C
ATOM   1921  CD2 LEU A 238       1.710  50.084  29.886  1.00 21.09           C
ATOM   1922  N   LYS A 239      -2.847  49.258  30.266  1.00 20.82           N
ATOM   1923  CA  LYS A 239      -3.870  48.282  30.679  1.00 22.77           C
ATOM   1924  C   LYS A 239      -3.328  47.309  31.739  1.00 20.78           C
ATOM   1925  O   LYS A 239      -3.987  47.045  32.750  1.00 21.34           O
ATOM   1926  CB  LYS A 239      -4.384  47.543  29.488  1.00 21.61           C
ATOM   1927  CG  LYS A 239      -5.167  48.489  28.511  1.00 27.26           C
ATOM   1928  CD  LYS A 239      -5.415  47.860  27.167  1.00 32.53           C
ATOM   1929  CE  LYS A 239      -6.495  48.640  26.409  1.00 37.38           C
ATOM   1930  NZ  LYS A 239      -7.504  47.716  25.779  1.00 41.05           N
ATOM   1931  N   ASN A 240      -2.106  46.829  31.541  1.00 19.71           N
ATOM   1932  CA  ASN A 240      -1.502  45.911  32.483  1.00 16.51           C
ATOM   1933  C   ASN A 240      -0.587  46.568  33.517  1.00 16.42           C
ATOM   1934  O   ASN A 240       0.449  46.046  33.833  1.00 18.50           O
ATOM   1935  CB  ASN A 240      -0.798  44.802  31.683  1.00 14.83           C
ATOM   1936  CG  ASN A 240      -1.822  43.905  30.979  1.00 18.91           C
ATOM   1937  OD1 ASN A 240      -2.307  42.942  31.542  1.00 19.99           O
ATOM   1938  ND2 ASN A 240      -2.196  44.271  29.777  1.00 23.25           N
ATOM   1939  N   SER A 241      -1.017  47.691  34.122  1.00 19.82           N
ATOM   1940  CA  SER A 241      -0.186  48.374  35.139  1.00 22.36           C
ATOM   1941  C   SER A 241       0.073  47.538  36.361  1.00 20.03           C
ATOM   1942  O   SER A 241       1.092  47.715  37.038  1.00 22.16           O
ATOM   1943  CB  SER A 241      -0.863  49.667  35.608  1.00 23.57           C
ATOM   1944  OG  SER A 241      -2.195  49.387  35.952  1.00 30.32           O
ATOM   1945  N   HIS A 242      -0.804  46.550  36.643  1.00 19.43           N
ATOM   1946  CA  HIS A 242      -0.605  45.730  37.847  1.00 19.11           C
ATOM   1947  C   HIS A 242       0.667  44.926  37.881  1.00 19.49           C
ATOM   1948  O   HIS A 242       1.145  44.552  38.944  1.00 23.78           O
ATOM   1949  CB  HIS A 242      -1.772  44.729  38.024  1.00 18.62           C
ATOM   1950  CG  HIS A 242      -1.887  43.770  36.862  1.00 15.38           C
ATOM   1951  ND1 HIS A 242      -1.310  42.510  36.850  1.00 20.24           N
ATOM   1952  CE1 HIS A 242      -1.534  41.950  35.665  1.00 13.20           C
ATOM   1953  NE2 HIS A 242      -2.175  42.813  34.906  1.00 17.21           N
ATOM   1954  CD2 HIS A 242      -2.438  43.948  35.645  1.00 13.10           C
ATOM   1955  N   LYS A 243       1.224  44.601  36.723  1.00 19.85           N
ATOM   1956  CA  LYS A 243       2.413  43.766  36.763  1.00 21.56           C
ATOM   1957  C   LYS A 243       3.695  44.535  36.475  1.00 19.39           C
ATOM   1958  O   LYS A 243       4.716  43.931  36.310  1.00 23.08           O
ATOM   1959  CB  LYS A 243       2.283  42.561  35.808  1.00 20.88           C
ATOM   1960  CG  LYS A 243       1.946  42.924  34.424  1.00 24.29           C
ATOM   1961  CD  LYS A 243       2.453  41.871  33.478  1.00 30.59           C
ATOM   1962  CE  LYS A 243       1.534  41.804  32.314  1.00 28.80           C
ATOM   1963  NZ  LYS A 243       1.938  40.724  31.322  1.00 28.74           N
ATOM   1964  N   VAL A 244       3.621  45.850  36.380  1.00 19.41           N
ATOM   1965  CA  VAL A 244       4.815  46.606  36.062  1.00 16.80           C
ATOM   1966  C   VAL A 244       5.405  47.177  37.356  1.00 16.94           C
ATOM   1967  O   VAL A 244       4.651  47.631  38.233  1.00 18.15           O
ATOM   1968  CB  VAL A 244       4.421  47.738  35.131  1.00 18.29           C
ATOM   1969  CG1 VAL A 244       5.628  48.612  34.818  1.00 21.72           C
ATOM   1970  CG2 VAL A 244       3.836  47.180  33.795  1.00 20.06           C
ATOM   1971  N   SER A 245       6.715  47.118  37.471  1.00 14.69           N
ATOM   1972  CA  SER A 245       7.394  47.704  38.626  1.00 16.91           C
ATOM   1973  C   SER A 245       7.158  49.203  38.760  1.00 17.10           C
ATOM   1974  O   SER A 245       6.910  49.922  37.795  1.00 16.02           O
ATOM   1975  CB  SER A 245       8.902  47.424  38.547  1.00 17.90           C
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FIGURE 4GG

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ATOM   1976  OG  SER A 245       9.504  48.195  37.526  1.00 18.08           O
ATOM   1977  N   PRO A 246       7.214  49.716  39.980  1.00 16.67           N
ATOM   1978  CA  PRO A 246       7.118  51.173  40.200  1.00 14.64           C
ATOM   1979  C   PRO A 246       8.177  51.918  39.359  1.00 14.70           C
ATOM   1980  O   PRO A 246       7.887  53.005  38.871  1.00 14.51           O
ATOM   1981  CB  PRO A 246       7.414  51.317  41.698  1.00 18.02           C
ATOM   1982  CG  PRO A 246       6.915  49.965  42.235  1.00 17.89           C
ATOM   1983  CD  PRO A 246       7.251  48.925  41.241  1.00 18.29           C
ATOM   1984  N   VAL A 247       9.374  51.359  39.222  1.00 13.22           N
ATOM   1985  CA  VAL A 247      10.449  52.099  38.503  1.00 12.85           C
ATOM   1986  C   VAL A 247      10.093  52.161  37.011  1.00 12.42           C
ATOM   1987  O   VAL A 247      10.277  53.224  36.388  1.00 12.80           O
ATOM   1988  CB  VAL A 247      11.884  51.542  38.753  1.00 14.14           C
ATOM   1989  CG1 VAL A 247      12.086  50.168  38.235  1.00 18.29           C
ATOM   1990  CG2 VAL A 247      12.907  52.418  38.115  1.00 14.93           C
ATOM   1991  N   LEU A 248       9.540  51.089  36.446  1.00 11.61           N
ATOM   1992  CA  LEU A 248       9.150  51.184  35.025  1.00 13.31           C
ATOM   1993  C   LEU A 248       7.915  52.081  34.843  1.00 12.97           C
ATOM   1994  O   LEU A 248       7.802  52.839  33.871  1.00 12.11           O
ATOM   1995  CB  LEU A 248       8.911  49.772  34.457  1.00 12.20           C
ATOM   1996  CG  LEU A 248       8.326  49.685  33.021  1.00 13.80           C
ATOM   1997  CD1 LEU A 248       9.131  50.550  32.019  1.00 14.35           C
ATOM   1998  CD2 LEU A 248       8.267  48.234  32.581  1.00 14.42           C
ATOM   1999  N   ARG A 249       6.974  52.039  35.773  1.00 11.52           N
ATOM   2000  CA  ARG A 249       5.834  52.925  35.706  1.00 12.62           C
ATOM   2001  C   ARG A 249       6.314  54.373  35.685  1.00 12.84           C
ATOM   2002  O   ARG A 249       5.770  55.174  34.952  1.00 13.05           O
ATOM   2003  CB BARG A 249       4.964  52.696  36.939  0.25 12.33           C
ATOM   2004  CB AARG A 249       4.877  52.678  36.870  0.75 15.56           C
ATOM   2005  CG BARG A 249       3.797  53.646  37.109  0.25  9.14           C
ATOM   2006  CG AARG A 249       4.161  51.326  36.750  0.75 19.29           C
ATOM   2007  CD BARG A 249       2.893  53.302  38.312  0.25 13.35           C
ATOM   2008  CD AARG A 249       3.017  51.120  37.779  0.75 26.93           C
ATOM   2009  NE BARG A 249       3.043  51.901  38.740  0.25 16.87           N
ATOM   2010  NE AARG A 249       1.812  51.867  37.355  0.75 32.91           N
ATOM   2011  CZ BARG A 249       3.362  51.483  39.972  0.25 18.67           C
ATOM   2012  CZ AARG A 249       0.748  52.123  38.125  0.75 34.19           C
ATOM   2013  NH1BARG A 249       3.472  50.177  40.212  0.25 16.90           N
ATOM   2014  NH1AARG A 249      -0.279  52.803  37.638  0.75 34.31           N
ATOM   2015  NH2BARG A 249       3.594  52.347  40.961  0.25 18.61           N
ATOM   2016  NH2AARG A 249       0.725  51.729  39.392  0.75 36.84           N
ATOM   2017  N   ASP A 250       7.312  54.701  36.518  1.00 12.28           N
ATOM   2018  CA  ASP A 250       7.816  56.067  36.612  1.00 12.79           C
ATOM   2019  C   ASP A 250       8.506  56.477  35.294  1.00 12.77           C
ATOM   2020  O   ASP A 250       8.312  57.585  34.787  1.00 13.07           O
ATOM   2021  CB  ASP A 250       8.836  56.190  37.717  1.00 14.77           C
ATOM   2022  CG  ASP A 250       9.263  57.632  37.892  1.00 20.60           C
ATOM   2023  OD1 ASP A 250      10.305  58.045  37.331  1.00 19.15           O
ATOM   2024  OD2 ASP A 250       8.584  58.473  38.545  1.00 26.42           O
ATOM   2025  N   PHE A 251       9.267  55.539  34.739  1.00 10.99           N
ATOM   2026  CA  PHE A 251       9.939  55.730  33.457  1.00 10.73           C
ATOM   2027  C   PHE A 251       8.889  56.060  32.372  1.00 11.00           C
ATOM   2028  O   PHE A 251       9.074  57.076  31.639  1.00 11.60           O
ATOM   2029  CB  PHE A 251      10.694  54.432  33.155  1.00 10.71           C
ATOM   2030  CG  PHE A 251      11.544  54.433  31.882  1.00 11.29           C
ATOM   2031  CD1 PHE A 251      12.829  54.963  31.890  1.00 11.44           C
ATOM   2032  CE1 PHE A 251      13.685  54.893  30.746  1.00 10.81           C
ATOM   2033  CZ  PHE A 251      13.245  54.234  29.630  1.00 12.41           C
ATOM   2034  CE2 PHE A 251      11.949  53.671  29.601  1.00 13.51           C
ATOM   2035  CD2 PHE A 251      11.108  53.752  30.772  1.00 13.44           C
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FIGURE 4HH

```
ATOM   2036  N   LEU A 252       7.841  55.248  32.255  1.00  9.80           N
ATOM   2037  CA  LEU A 252       6.833  55.548  31.246  1.00 10.32           C
ATOM   2038  C   LEU A 252       6.125  56.878  31.483  1.00 11.26           C
ATOM   2039  O   LEU A 252       5.794  57.604  30.532  1.00 10.20           O
ATOM   2040  CB  LEU A 252       5.785  54.407  31.248  1.00 12.14           C
ATOM   2041  CG  LEU A 252       4.708  54.485  30.197  1.00 13.13           C
ATOM   2042  CD1 LEU A 252       5.347  54.707  28.781  1.00 15.70           C
ATOM   2043  CD2 LEU A 252       3.896  53.133  30.265  1.00 17.25           C
ATOM   2044  N   GLU A 253       5.822  57.185  32.742  1.00 10.95           N
ATOM   2045  CA  GLU A 253       5.103  58.425  33.061  1.00 12.42           C
ATOM   2046  C   GLU A 253       5.942  59.671  32.803  1.00 12.33           C
ATOM   2047  O   GLU A 253       5.362  60.772  32.693  1.00 16.37           O
ATOM   2048  CB  GLU A 253       4.692  58.405  34.553  1.00 14.53           C
ATOM   2049  CG  GLU A 253       3.477  57.515  34.759  1.00 19.54           C
ATOM   2050  CD  GLU A 253       3.160  57.256  36.242  1.00 29.82           C
ATOM   2051  OE1 GLU A 253       3.821  57.837  37.129  1.00 35.97           O
ATOM   2052  OE2 GLU A 253       2.247  56.445  36.507  1.00 35.79           O
ATOM   2053  N   ARG A 254       7.268  59.501  32.658  1.00 10.94           N
ATOM   2054  CA  ARG A 254       8.090  60.616  32.211  1.00  9.95           C
ATOM   2055  C   ARG A 254       8.027  60.827  30.685  1.00 10.51           C
ATOM   2056  O   ARG A 254       8.375  61.885  30.209  1.00 11.14           O
ATOM   2057  CB  ARG A 254       9.552  60.414  32.587  1.00 10.09           C
ATOM   2058  CG  ARG A 254       9.801  60.451  34.150  1.00 11.47           C
ATOM   2059  CD  ARG A 254       9.585  61.896  34.720  1.00 12.76           C
ATOM   2060  NE  ARG A 254      10.392  62.945  34.055  1.00 12.48           N
ATOM   2061  CZ  ARG A 254       9.880  64.010  33.407  1.00  9.08           C
ATOM   2062  NH1 ARG A 254      10.713  64.865  32.868  1.00 11.66           N
ATOM   2063  NH2 ARG A 254       8.550  64.208  33.253  1.00 13.63           N
ATOM   2064  N   MET A 255       7.539  59.824  29.947  1.00  8.84           N
ATOM   2065  CA  MET A 255       7.472  59.927  28.467  1.00  9.29           C
ATOM   2066  C   MET A 255       6.090  60.424  28.029  1.00  8.46           C
ATOM   2067  O   MET A 255       5.971  61.269  27.125  1.00  9.32           O
ATOM   2068  CB BMET A 255       7.752  58.542  27.828  0.35  8.95           C
ATOM   2069  CB AMET A 255       7.757  58.552  27.856  0.65  8.59           C
ATOM   2070  CG BMET A 255       9.033  57.829  28.294  0.35 11.26           C
ATOM   2071  CG AMET A 255       9.150  58.127  28.125  0.65 11.34           C
ATOM   2072  SD BMET A 255       9.118  56.082  27.725  0.35 13.20           S
ATOM   2073  SD AMET A 255       9.526  56.749  27.065  0.65 13.97           S
ATOM   2074  CE BMET A 255      10.893  55.888  27.580  0.35 16.06           C
ATOM   2075  CE AMET A 255      10.390  55.756  28.119  0.65 18.05           C
ATOM   2076  N   LEU A 256       5.034  59.862  28.628  1.00 10.19           N
ATOM   2077  CA  LEU A 256       3.666  60.149  28.232  1.00  9.88           C
ATOM   2078  C   LEU A 256       3.121  61.321  29.051  1.00 10.86           C
ATOM   2079  O   LEU A 256       2.355  61.175  30.010  1.00 12.08           O
ATOM   2080  CB  LEU A 256       2.758  58.918  28.325  1.00 10.28           C
ATOM   2081  CG  LEU A 256       3.237  57.810  27.377  1.00 10.63           C
ATOM   2082  CD1 LEU A 256       2.377  56.581  27.568  1.00 13.07           C
ATOM   2083  CD2 LEU A 256       3.116  58.340  25.984  1.00 10.61           C
ATOM   2084  N   VAL A 257       3.640  62.466  28.706  1.00  8.53           N
ATOM   2085  CA  VAL A 257       3.300  63.746  29.395  1.00  9.01           C
ATOM   2086  C   VAL A 257       2.833  64.692  28.296  1.00  9.52           C
ATOM   2087  O   VAL A 257       3.571  64.833  27.280  1.00  9.82           O
ATOM   2088  CB  VAL A 257       4.611  64.285  29.994  1.00 12.13           C
ATOM   2089  CG1 VAL A 257       4.413  65.721  30.554  1.00 12.60           C
ATOM   2090  CG2 VAL A 257       5.102  63.361  31.078  1.00 12.28           C
ATOM   2091  N   ARG A 258       1.646  65.310  28.409  1.00  8.71           N
ATOM   2092  CA  ARG A 258       1.168  66.205  27.365  1.00  8.96           C
ATOM   2093  C   ARG A 258       2.057  67.397  27.157  1.00 11.25           C
ATOM   2094  O   ARG A 258       2.288  67.770  25.973  1.00 12.22           O
ATOM   2095  CB  ARG A 258      -0.290  66.685  27.603  1.00  9.62           C
```

FIGURE 4II

ATOM	2096	CG	ARG	A	258	-1.362	65.599	27.476	1.00	12.12	C
ATOM	2097	CD	ARG	A	258	-2.794	66.123	27.569	1.00	12.75	C
ATOM	2098	NE	ARG	A	258	-2.981	67.106	26.533	1.00	11.22	N
ATOM	2099	CZ	ARG	A	258	-3.287	66.808	25.262	1.00	9.89	C
ATOM	2100	NH1	ARG	A	258	-3.572	65.537	24.905	1.00	9.72	N
ATOM	2101	NH2	ARG	A	258	-3.353	67.801	24.365	1.00	11.46	N
ATOM	2102	N	ASP	A	259	2.481	68.043	28.259	1.00	10.31	N
ATOM	2103	CA	ASP	A	259	3.277	69.275	28.096	1.00	13.08	C
ATOM	2104	C	ASP	A	259	4.669	68.911	27.622	1.00	11.76	C
ATOM	2105	O	ASP	A	259	5.389	68.196	28.324	1.00	11.51	O
ATOM	2106	CB	ASP	A	259	3.367	70.018	29.459	1.00	13.39	C
ATOM	2107	CG	ASP	A	259	4.096	71.349	29.380	1.00	23.83	C
ATOM	2108	OD1	ASP	A	259	4.843	71.624	28.427	1.00	27.23	O
ATOM	2109	OD2	ASP	A	259	3.974	72.190	30.300	1.00	28.54	O
ATOM	2110	N	PRO	A	260	5.055	69.328	26.428	1.00	12.33	N
ATOM	2111	CA	PRO	A	260	6.360	68.882	25.908	1.00	13.56	C
ATOM	2112	C	PRO	A	260	7.544	69.396	26.697	1.00	16.64	C
ATOM	2113	O	PRO	A	260	8.579	68.730	26.620	1.00	17.54	O
ATOM	2114	CB	PRO	A	260	6.421	69.440	24.460	1.00	14.17	C
ATOM	2115	CG	PRO	A	260	5.067	70.008	24.211	1.00	18.15	C
ATOM	2116	CD	PRO	A	260	4.284	70.159	25.491	1.00	13.55	C
ATOM	2117	N	GLN	A	261	7.421	70.543	27.408	1.00	16.15	N
ATOM	2118	CA	GLN	A	261	8.545	71.085	28.213	1.00	18.11	C
ATOM	2119	C	GLN	A	261	8.695	70.252	29.500	1.00	17.29	C
ATOM	2120	O	GLN	A	261	9.810	70.189	30.053	1.00	20.10	O
ATOM	2121	CB	GLN	A	261	8.319	72.578	28.568	1.00	19.35	C
ATOM	2122	CG	GLN	A	261	8.482	73.464	27.326	1.00	26.81	C
ATOM	2123	CD	GLN	A	261	7.829	74.848	27.425	1.00	36.36	C
ATOM	2124	OE1	GLN	A	261	7.680	75.425	28.518	1.00	42.01	O
ATOM	2125	NE2	GLN	A	261	7.439	75.385	26.268	1.00	39.98	N
ATOM	2126	N	GLU	A	262	7.614	69.610	29.951	1.00	13.53	N
ATOM	2127	CA	GLU	A	262	7.673	68.770	31.175	1.00	12.61	C
ATOM	2128	C	GLU	A	262	8.098	67.311	30.859	1.00	12.36	C
ATOM	2129	O	GLU	A	262	8.604	66.568	31.693	1.00	12.06	O
ATOM	2130	CB	BGLU	A	262	6.378	68.867	31.979	0.25	13.67	C
ATOM	2131	CB	AGLU	A	262	6.252	68.712	31.755	0.75	13.17	C
ATOM	2132	CG	BGLU	A	262	6.058	70.315	32.350	0.25	16.05	C
ATOM	2133	CG	AGLU	A	262	5.999	67.839	33.001	0.75	20.15	C
ATOM	2134	CD	BGLU	A	262	5.380	70.491	33.692	0.25	20.99	C
ATOM	2135	CD	AGLU	A	262	4.499	67.713	33.426	0.75	23.66	C
ATOM	2136	OE1	BGLU	A	262	4.275	69.946	33.881	0.25	22.46	O
ATOM	2137	OE1	AGLU	A	262	3.605	68.438	32.919	0.75	23.00	O
ATOM	2138	OE2	BGLU	A	262	5.950	71.192	34.569	0.25	22.29	O
ATOM	2139	OE2	AGLU	A	262	4.185	66.828	34.253	0.75	26.78	O
ATOM	2140	N	ARG	A	263	7.836	66.916	29.632	1.00	11.27	N
ATOM	2141	CA	ARG	A	263	8.249	65.608	29.151	1.00	10.67	C
ATOM	2142	C	ARG	A	263	9.746	65.363	29.276	1.00	9.00	C
ATOM	2143	O	ARG	A	263	10.577	66.241	29.034	1.00	11.31	O
ATOM	2144	CB	ARG	A	263	7.799	65.513	27.666	1.00	10.63	C
ATOM	2145	CG	ARG	A	263	7.801	64.050	27.142	1.00	9.46	C
ATOM	2146	CD	ARG	A	263	7.252	63.895	25.701	1.00	8.86	C
ATOM	2147	NE	ARG	A	263	5.920	64.511	25.624	1.00	8.65	N
ATOM	2148	CZ	ARG	A	263	5.430	65.131	24.541	1.00	7.25	C
ATOM	2149	NH1	ARG	A	263	4.223	65.712	24.568	1.00	7.82	N
ATOM	2150	NH2	ARG	A	263	6.197	65.162	23.396	1.00	7.55	N
ATOM	2151	N	ALA	A	264	10.141	64.130	29.617	1.00	9.24	N
ATOM	2152	CA	ALA	A	264	11.569	63.790	29.689	1.00	8.75	C
ATOM	2153	C	ALA	A	264	12.282	63.886	28.329	1.00	10.29	C
ATOM	2154	O	ALA	A	264	11.652	63.654	27.278	1.00	12.39	O
ATOM	2155	CB	ALA	A	264	11.769	62.358	30.245	1.00	10.59	C

FIGURE 4JJ

```
ATOM   2156  N   THR A 265      13.555  64.303  28.364  1.00 12.07           N
ATOM   2157  CA  THR A 265      14.397  64.195  27.178  1.00 11.22           C
ATOM   2158  C   THR A 265      15.015  62.814  27.145  1.00  9.84           C
ATOM   2159  O   THR A 265      15.014  62.018  28.127  1.00 10.00           O
ATOM   2160  CB  THR A 265      15.537  65.184  27.215  1.00 11.32           C
ATOM   2161  OG1 THR A 265      16.342  64.868  28.387  1.00 14.65           O
ATOM   2162  CG2 THR A 265      15.021  66.639  27.343  1.00 12.42           C
ATOM   2163  N   ALA A 266      15.579  62.451  25.973  1.00  9.51           N
ATOM   2164  CA  ALA A 266      16.215  61.130  25.850  1.00  9.32           C
ATOM   2165  C   ALA A 266      17.363  60.981  26.851  1.00  9.81           C
ATOM   2166  O   ALA A 266      17.492  59.932  27.449  1.00 12.03           O
ATOM   2167  CB  ALA A 266      16.742  60.880  24.384  1.00  8.46           C
ATOM   2168  N   GLN A 267      18.132  62.052  27.079  1.00 11.17           N
ATOM   2169  CA  GLN A 267      19.220  61.971  28.012  1.00 11.55           C
ATOM   2170  C   GLN A 267      18.700  61.745  29.444  1.00 12.69           C
ATOM   2171  O   GLN A 267      19.280  60.937  30.197  1.00 13.32           O
ATOM   2172  CB  GLN A 267      20.064  63.257  27.967  1.00 14.77           C
ATOM   2173  CG  GLN A 267      21.347  63.092  28.828  1.00 17.49           C
ATOM   2174  CD  GLN A 267      22.231  61.940  28.381  1.00 18.90           C
ATOM   2175  OE1 GLN A 267      22.614  61.897  27.218  1.00 18.69           O
ATOM   2176  NE2 GLN A 267      22.513  60.975  29.283  1.00 18.42           N
ATOM   2177  N   GLU A 268      17.615  62.418  29.820  1.00 11.27           N
ATOM   2178  CA  GLU A 268      17.057  62.158  31.178  1.00 12.74           C
ATOM   2179  C   GLU A 268      16.644  60.672  31.358  1.00 11.29           C
ATOM   2180  O   GLU A 268      16.904  60.027  32.396  1.00 13.40           O
ATOM   2181  CB  GLU A 268      15.842  63.090  31.443  1.00 11.01           C
ATOM   2182  CG  GLU A 268      15.255  62.851  32.880  1.00 14.18           C
ATOM   2183  CD  GLU A 268      13.938  63.542  33.201  1.00 18.01           C
ATOM   2184  OE1 GLU A 268      13.241  63.063  34.149  1.00 17.51           O
ATOM   2185  OE2 GLU A 268      13.572  64.501  32.526  1.00 18.85           O
ATOM   2186  N   LEU A 269      16.054  60.103  30.306  1.00 10.15           N
ATOM   2187  CA  LEU A 269      15.645  58.723  30.362  1.00  9.80           C
ATOM   2188  C   LEU A 269      16.850  57.766  30.401  1.00 10.14           C
ATOM   2189  O   LEU A 269      16.814  56.743  31.090  1.00 11.10           O
ATOM   2190  CB  LEU A 269      14.716  58.393  29.167  1.00  9.81           C
ATOM   2191  CG  LEU A 269      13.407  59.175  29.265  1.00 10.43           C
ATOM   2192  CD1 LEU A 269      12.754  59.204  27.883  1.00 11.29           C
ATOM   2193  CD2 LEU A 269      12.411  58.599  30.348  1.00 12.24           C
ATOM   2194  N   LEU A 270      17.920  58.083  29.681  1.00 11.42           N
ATOM   2195  CA  LEU A 270      19.140  57.290  29.768  1.00 11.94           C
ATOM   2196  C   LEU A 270      19.687  57.253  31.204  1.00 13.97           C
ATOM   2197  O   LEU A 270      20.327  56.258  31.621  1.00 14.83           O
ATOM   2198  CB  LEU A 270      20.213  57.866  28.835  1.00 13.11           C
ATOM   2199  CG  LEU A 270      20.063  57.427  27.368  1.00 12.33           C
ATOM   2200  CD1 LEU A 270      21.227  58.082  26.641  1.00 12.47           C
ATOM   2201  CD2 LEU A 270      20.149  55.866  27.222  1.00 12.27           C
ATOM   2202  N   ASP A 271      19.422  58.327  31.945  1.00 11.74           N
ATOM   2203  CA  ASP A 271      19.906  58.455  33.300  1.00 14.17           C
ATOM   2204  C   ASP A 271      18.970  57.850  34.345  1.00 14.46           C
ATOM   2205  O   ASP A 271      19.232  57.956  35.560  1.00 15.38           O
ATOM   2206  CB  ASP A 271      20.095  59.949  33.608  1.00 14.67           C
ATOM   2207  CG  ASP A 271      21.229  60.589  32.795  1.00 18.70           C
ATOM   2208  OD1 ASP A 271      22.119  59.824  32.328  1.00 21.12           O
ATOM   2209  OD2 ASP A 271      21.299  61.831  32.586  1.00 21.41           O
ATOM   2210  N   HIS A 272      17.863  57.263  33.895  1.00 12.27           N
ATOM   2211  CA  HIS A 272      16.794  56.833  34.812  1.00 12.23           C
ATOM   2212  C   HIS A 272      17.131  55.483  35.410  1.00 12.60           C
ATOM   2213  O   HIS A 272      17.663  54.598  34.699  1.00 13.50           O
ATOM   2214  CB  HIS A 272      15.508  56.658  34.012  1.00 12.53           C
ATOM   2215  CG  HIS A 272      14.277  56.535  34.846  1.00 12.61           C
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FIGURE 4KK

ATOM	2216	ND1	HIS	A	272	13.874	55.337	35.396	1.00	10.96	N
ATOM	2217	CE1	HIS	A	272	12.725	55.521	36.031	1.00	10.40	C
ATOM	2218	NE2	HIS	A	272	12.404	56.810	35.965	1.00	11.35	N
ATOM	2219	CD2	HIS	A	272	13.348	57.462	35.211	1.00	11.85	C
ATOM	2220	N	PRO	A	273	16.784	55.235	36.675	1.00	13.62	N
ATOM	2221	CA	PRO	A	273	17.104	53.947	37.300	1.00	14.95	C
ATOM	2222	C	PRO	A	273	16.476	52.713	36.645	1.00	12.35	C
ATOM	2223	O	PRO	A	273	17.017	51.628	36.825	1.00	14.80	O
ATOM	2224	CB	PRO	A	273	16.608	54.102	38.752	1.00	16.16	C
ATOM	2225	CG	PRO	A	273	16.095	55.471	38.910	1.00	19.63	C
ATOM	2226	CD	PRO	A	273	16.166	56.217	37.604	1.00	15.13	C
ATOM	2227	N	PHE	A	274	15.432	52.854	35.821	1.00	11.42	N
ATOM	2228	CA	PHE	A	274	14.877	51.667	35.176	1.00	12.37	C
ATOM	2229	C	PHE	A	274	15.995	51.014	34.323	1.00	11.96	C
ATOM	2230	O	PHE	A	274	16.050	49.765	34.208	1.00	14.11	O
ATOM	2231	CB	PHE	A	274	13.670	52.047	34.269	1.00	12.80	C
ATOM	2232	CG	PHE	A	274	13.199	50.896	33.425	1.00	10.87	C
ATOM	2233	CD1	PHE	A	274	12.766	49.719	34.015	1.00	13.43	C
ATOM	2234	CE1	PHE	A	274	12.321	48.643	33.226	1.00	15.05	C
ATOM	2235	CZ	PHE	A	274	12.331	48.723	31.854	1.00	13.17	C
ATOM	2236	CE2	PHE	A	274	12.761	49.862	31.235	1.00	12.76	C
ATOM	2237	CD2	PHE	A	274	13.184	50.990	32.026	1.00	12.05	C
ATOM	2238	N	LEU	A	275	16.819	51.836	33.675	1.00	13.51	N
ATOM	2239	CA	LEU	A	275	17.850	51.318	32.797	1.00	16.21	C
ATOM	2240	C	LEU	A	275	19.018	50.613	33.506	1.00	18.22	C
ATOM	2241	O	LEU	A	275	19.859	50.023	32.852	1.00	19.03	O
ATOM	2242	CB	LEU	A	275	18.305	52.335	31.758	1.00	15.72	C
ATOM	2243	CG	LEU	A	275	17.136	52.823	30.875	1.00	16.68	C
ATOM	2244	CD1	LEU	A	275	17.697	53.751	29.816	1.00	16.32	C
ATOM	2245	CD2	LEU	A	275	16.396	51.667	30.195	1.00	15.77	C
ATOM	2246	N	LEU	A	276	19.008	50.599	34.851	1.00	19.65	N
ATOM	2247	CA	LEU	A	276	19.892	49.652	35.576	1.00	21.14	C
ATOM	2248	C	LEU	A	276	19.523	48.202	35.304	1.00	20.14	C
ATOM	2249	O	LEU	A	276	20.318	47.290	35.571	1.00	21.20	O
ATOM	2250	CB	LEU	A	276	19.830	49.899	37.085	1.00	20.89	C
ATOM	2251	CG	LEU	A	276	20.178	51.328	37.553	1.00	24.72	C
ATOM	2252	CD1	LEU	A	276	19.809	51.445	39.036	1.00	27.85	C
ATOM	2253	CD2	LEU	A	276	21.636	51.683	37.306	1.00	27.39	C
ATOM	2254	N	GLN	A	277	18.310	47.961	34.802	1.00	18.01	N
ATOM	2255	CA	GLN	A	277	17.825	46.626	34.468	1.00	19.00	C
ATOM	2256	C	GLN	A	277	18.214	46.131	33.074	1.00	19.15	C
ATOM	2257	O	GLN	A	277	17.840	45.013	32.705	1.00	18.88	O
ATOM	2258	CB	GLN	A	277	16.292	46.543	34.633	1.00	19.70	C
ATOM	2259	CG	GLN	A	277	15.883	46.521	36.112	1.00	22.51	C
ATOM	2260	CD	GLN	A	277	14.415	46.848	36.339	1.00	24.20	C
ATOM	2261	OE1	GLN	A	277	14.078	47.918	36.866	1.00	26.83	O
ATOM	2262	NE2	GLN	A	277	13.535	45.924	35.952	1.00	28.13	N
ATOM	2263	N	THR	A	278	18.987	46.926	32.331	1.00	17.92	N
ATOM	2264	CA	THR	A	278	19.324	46.608	30.905	1.00	21.03	C
ATOM	2265	C	THR	A	278	20.091	45.284	30.863	1.00	22.47	C
ATOM	2266	O	THR	A	278	20.978	45.061	31.704	1.00	24.27	O
ATOM	2267	CB	THR	A	278	20.169	47.742	30.294	1.00	20.39	C
ATOM	2268	OG1	THR	A	278	19.426	48.972	30.304	1.00	23.31	O
ATOM	2269	CG2	THR	A	278	20.419	47.550	28.813	1.00	23.41	C
ATOM	2270	N	GLY	A	279	19.736	44.380	29.952	1.00	23.07	N
ATOM	2271	CA	GLY	A	279	20.435	43.089	29.864	1.00	25.39	C
ATOM	2272	C	GLY	A	279	21.391	43.132	28.691	1.00	26.73	C
ATOM	2273	O	GLY	A	279	21.547	44.179	28.045	1.00	27.80	O
ATOM	2274	N	LEU	A	280	22.015	42.005	28.400	1.00	29.48	N
ATOM	2275	CA	LEU	A	280	22.946	41.920	27.268	1.00	30.73	C

FIGURE 4LL

```
ATOM   2276  C   LEU A 280      22.130  41.621  26.034  1.00 30.92           C
ATOM   2277  O   LEU A 280      21.051  41.067  26.157  1.00 30.61           O
ATOM   2278  CB  LEU A 280      23.924  40.779  27.495  1.00 31.98           C
ATOM   2279  CG  LEU A 280      24.759  40.843  28.764  1.00 33.36           C
ATOM   2280  CD1 LEU A 280      25.426  39.482  29.016  1.00 39.58           C
ATOM   2281  CD2 LEU A 280      25.784  41.945  28.642  1.00 36.61           C
ATOM   2282  N   PRO A 281      22.629  41.991  24.851  1.00 33.08           N
ATOM   2283  CA  PRO A 281      21.961  41.634  23.583  1.00 33.40           C
ATOM   2284  C   PRO A 281      21.477  40.190  23.544  1.00 33.26           C
ATOM   2285  O   PRO A 281      20.406  39.902  22.974  1.00 31.95           O
ATOM   2286  CB  PRO A 281      23.074  41.836  22.544  1.00 34.90           C
ATOM   2287  CG  PRO A 281      23.899  42.993  23.120  1.00 33.86           C
ATOM   2288  CD  PRO A 281      23.826  42.835  24.624  1.00 33.62           C
ATOM   2289  N   GLU A 282      22.240  39.289  24.163  1.00 32.07           N
ATOM   2290  CA  GLU A 282      21.864  37.893  24.200  1.00 31.48           C
ATOM   2291  C   GLU A 282      20.517  37.618  24.865  1.00 29.03           C
ATOM   2292  O   GLU A 282      19.957  36.575  24.594  1.00 30.91           O
ATOM   2293  CB  GLU A 282      22.945  37.028  24.854  1.00 34.18           C
ATOM   2294  CG  GLU A 282      24.324  37.165  24.217  1.00 39.89           C
ATOM   2295  CD  GLU A 282      25.183  38.200  24.943  1.00 44.46           C
ATOM   2296  OE1 GLU A 282      25.705  37.875  26.044  1.00 47.77           O
ATOM   2297  OE2 GLU A 282      25.322  39.337  24.418  1.00 44.88           O
ATOM   2298  N   CYS A 283      19.975  38.526  25.700  1.00 26.92           N
ATOM   2299  CA  CYS A 283      18.639  38.290  26.281  1.00 26.38           C
ATOM   2300  C   CYS A 283      17.524  38.297  25.240  1.00 24.27           C
ATOM   2301  O   CYS A 283      16.415  37.821  25.516  1.00 25.85           O
ATOM   2302  CB  CYS A 283      18.279  39.240  27.453  1.00 26.62           C
ATOM   2303  SG  CYS A 283      17.905  41.001  27.096  1.00 29.93           S
ATOM   2304  N   LEU A 284      17.806  38.854  24.056  1.00 20.18           N
ATOM   2305  CA  LEU A 284      16.806  38.882  22.984  1.00 18.11           C
ATOM   2306  C   LEU A 284      16.984  37.754  21.954  1.00 16.18           C
ATOM   2307  O   LEU A 284      16.094  37.498  21.159  1.00 17.35           O
ATOM   2308  CB  LEU A 284      16.833  40.239  22.252  1.00 18.37           C
ATOM   2309  CG  LEU A 284      16.534  41.433  23.168  1.00 19.77           C
ATOM   2310  CD1 LEU A 284      16.680  42.728  22.354  1.00 23.74           C
ATOM   2311  CD2 LEU A 284      15.121  41.313  23.726  1.00 20.69           C
ATOM   2312  N   VAL A 285      18.127  37.086  21.953  1.00 15.08           N
ATOM   2313  CA  VAL A 285      18.468  36.247  20.833  1.00 15.31           C
ATOM   2314  C   VAL A 285      17.519  35.038  20.690  1.00 15.94           C
ATOM   2315  O   VAL A 285      17.107  34.683  19.589  1.00 17.34           O
ATOM   2316  CB  VAL A 285      19.973  35.825  20.905  1.00 16.94           C
ATOM   2317  CG1 VAL A 285      20.270  34.706  19.900  1.00 16.98           C
ATOM   2318  CG2 VAL A 285      20.854  37.019  20.602  1.00 18.86           C
ATOM   2319  N   PRO A 286      17.176  34.351  21.762  1.00 18.00           N
ATOM   2320  CA  PRO A 286      16.255  33.206  21.583  1.00 19.06           C
ATOM   2321  C   PRO A 286      14.907  33.608  20.978  1.00 17.63           C
ATOM   2322  O   PRO A 286      14.346  32.870  20.174  1.00 18.09           O
ATOM   2323  CB  PRO A 286      16.073  32.652  22.991  1.00 20.10           C
ATOM   2324  CG  PRO A 286      17.314  33.136  23.719  1.00 21.99           C
ATOM   2325  CD  PRO A 286      17.682  34.479  23.137  1.00 20.86           C
ATOM   2326  N   LEU A 287      14.389  34.773  21.373  1.00 15.33           N
ATOM   2327  CA  LEU A 287      13.149  35.217  20.756  1.00 15.70           C
ATOM   2328  C   LEU A 287      13.270  35.574  19.285  1.00 14.54           C
ATOM   2329  O   LEU A 287      12.375  35.288  18.484  1.00 16.05           O
ATOM   2330  CB  LEU A 287      12.562  36.392  21.550  1.00 14.49           C
ATOM   2331  CG  LEU A 287      12.067  36.039  22.972  1.00 17.22           C
ATOM   2332  CD1 LEU A 287      11.677  37.326  23.670  1.00 17.60           C
ATOM   2333  CD2 LEU A 287      10.902  35.071  22.931  1.00 18.92           C
ATOM   2334  N   ILE A 288      14.386  36.211  18.943  1.00 13.83           N
ATOM   2335  CA  ILE A 288      14.626  36.573  17.566  1.00 16.13           C
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FIGURE 4MM

```
ATOM   2336  C   ILE A 288      14.615  35.278  16.745  1.00 16.83           C
ATOM   2337  O   ILE A 288      13.996  35.238  15.695  1.00 18.71           O
ATOM   2338  CB  ILE A 288      15.959  37.356  17.463  1.00 14.80           C
ATOM   2339  CG1 ILE A 288      15.758  38.765  18.063  1.00 15.30           C
ATOM   2340  CD1 ILE A 288      17.100  39.467  18.324  1.00 15.82           C
ATOM   2341  CG2 ILE A 288      16.405  37.438  15.992  1.00 18.31           C
ATOM   2342  N   GLN A 289      15.263  34.231  17.252  1.00 18.22           N
ATOM   2343  CA  GLN A 289      15.311  32.953  16.534  1.00 21.15           C
ATOM   2344  C   GLN A 289      13.922  32.317  16.398  1.00 23.19           C
ATOM   2345  O   GLN A 289      13.591  31.793  15.341  1.00 25.06           O
ATOM   2346  CB  GLN A 289      16.339  32.008  17.165  1.00 24.24           C
ATOM   2347  CG  GLN A 289      17.761  32.543  17.075  1.00 29.01           C
ATOM   2348  CD  GLN A 289      18.830  31.706  17.798  1.00 37.48           C
ATOM   2349  OE1 GLN A 289      18.536  30.948  18.737  1.00 39.07           O
ATOM   2350  NE2 GLN A 289      20.090  31.872  17.370  1.00 37.51           N
ATOM   2351  N   LEU A 290      13.073  32.426  17.425  1.00 21.62           N
ATOM   2352  CA  LEU A 290      11.710  31.851  17.323  1.00 22.73           C
ATOM   2353  C   LEU A 290      10.745  32.583  16.397  1.00 23.02           C
ATOM   2354  O   LEU A 290       9.826  31.970  15.843  1.00 24.60           O
ATOM   2355  CB  LEU A 290      11.117  31.720  18.726  1.00 22.22           C
ATOM   2356  CG  LEU A 290      11.829  30.696  19.606  1.00 25.78           C
ATOM   2357  CD1 LEU A 290      11.312  30.809  21.029  1.00 25.45           C
ATOM   2358  CD2 LEU A 290      11.590  29.257  18.993  1.00 29.01           C
ATOM   2359  N   TYR A 291      10.932  33.885  16.233  1.00 20.52           N
ATOM   2360  CA  TYR A 291       9.953  34.729  15.550  1.00 20.95           C
ATOM   2361  C   TYR A 291      10.362  35.555  14.303  1.00 25.40           C
ATOM   2362  O   TYR A 291       9.479  36.057  13.635  1.00 27.58           O
ATOM   2363  CB  TYR A 291       9.326  35.709  16.548  1.00 17.96           C
ATOM   2364  CG  TYR A 291       8.504  35.040  17.616  1.00 12.71           C
ATOM   2365  CD1 TYR A 291       9.009  34.877  18.896  1.00 11.98           C
ATOM   2366  CE1 TYR A 291       8.225  34.231  19.885  1.00 12.13           C
ATOM   2367  CZ  TYR A 291       6.957  33.787  19.540  1.00 11.48           C
ATOM   2368  OH  TYR A 291       6.155  33.157  20.474  1.00 13.73           O
ATOM   2369  CE2 TYR A 291       6.433  33.938  18.276  1.00 14.58           C
ATOM   2370  CD2 TYR A 291       7.211  34.574  17.317  1.00 17.15           C
ATOM   2371  N   ARG A 292      11.644  35.824  14.051  1.00 31.50           N
ATOM   2372  CA  ARG A 292      11.994  36.769  12.931  1.00 36.97           C
ATOM   2373  C   ARG A 292      11.375  36.347  11.582  1.00 39.86           C
ATOM   2374  O   ARG A 292      10.925  37.195  10.795  1.00 43.25           O
ATOM   2375  CB  ARG A 292      13.515  36.954  12.783  1.00 37.31           C
ATOM   2376  CG  ARG A 292      14.222  35.745  12.154  1.00 38.16           C
ATOM   2377  CD  ARG A 292      15.723  35.726  12.304  1.00 41.67           C
ATOM   2378  NE  ARG A 292      16.266  34.515  11.674  1.00 43.48           N
ATOM   2379  CZ  ARG A 292      16.717  34.461  10.419  1.00 44.76           C
ATOM   2380  NH1 ARG A 292      17.173  33.320   9.938  1.00 45.90           N
ATOM   2381  NH2 ARG A 292      16.724  35.545   9.643  1.00 43.30           N
ATOM   2382  N   LYS A 293      11.425  35.040  11.329  1.00 42.64           N
ATOM   2383  CA  LYS A 293      10.654  34.344  10.322  1.00 45.60           C
ATOM   2384  C   LYS A 293      10.390  32.998  10.996  1.00 47.37           C
ATOM   2385  O   LYS A 293      10.933  32.729  12.081  1.00 47.49           O
ATOM   2386  CB  LYS A 293      11.435  34.165   9.003  1.00 46.86           C
TER    2387      LYS A 293
ATOM   2388  N   GLY W   1       1.793  46.757  18.751  1.00 17.14           N
ATOM   2389  CA  GLY W   1       1.528  46.556  17.315  1.00 25.77           C
ATOM   2390  C   GLY W   1       0.951  45.176  17.042  1.00 29.23           C
ATOM   2391  O   GLY W   1       0.843  44.363  17.993  1.00 28.85           O
ATOM   2392  OXT GLY W   1       0.621  44.889  15.838  1.00 32.49           O
HETATM 2393  O   HOH W   2      22.188  40.692  11.498  1.00 11.89           O
HETATM 2394  O   HOH W   3      15.794  64.253  23.801  1.00  9.88           O
HETATM 2395  O   HOH W   4       8.355  59.596  16.556  1.00 10.82           O
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FIGURE 4NN

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HETATM 2396  O   HOH W   5       0.251  58.665  20.369  1.00 10.14           O
HETATM 2397  O   HOH W   6      -3.377  61.809  24.836  1.00 13.83           O
HETATM 2398  O   HOH W   7       5.153  62.069  17.436  1.00 12.04           O
HETATM 2399  O   HOH W   8      10.941  58.764  10.011  1.00 13.04           O
HETATM 2400  O   HOH W   9      12.472  67.030   6.773  1.00 14.71           O
HETATM 2401  O   HOH W  10      20.528  64.429  23.559  1.00 14.36           O
HETATM 2402  O   HOH W  11      24.360  54.889  11.681  1.00 11.45           O
HETATM 2403  O   HOH W  12      10.807  76.885  12.998  1.00 18.42           O
HETATM 2404  O   HOH W  13      11.294  63.640   5.849  1.00 13.10           O
HETATM 2405  O   HOH W  14      13.839  66.279  23.729  1.00 15.51           O
HETATM 2406  O   HOH W  15      18.311  64.329  25.078  1.00 13.78           O
HETATM 2407  O   HOH W  16       0.285  65.141  30.954  1.00 12.28           O
HETATM 2408  O   HOH W  17      27.953  46.434 -10.447  1.00 13.76           O
HETATM 2409  O   HOH W  18      11.595  65.584  25.348  1.00 16.11           O
HETATM 2410  O   HOH W  19      17.388  65.851 -14.665  1.00 20.06           O
HETATM 2411  O   HOH W  20       6.621  42.678  24.591  1.00 15.50           O
HETATM 2412  O   HOH W  21       1.428  67.642  30.959  1.00 14.12           O
HETATM 2413  O   HOH W  22      16.273  60.020  35.189  1.00 17.00           O
HETATM 2414  O   HOH W  23       4.051  58.864  14.885  1.00 15.77           O
HETATM 2415  O   HOH W  24       3.980  43.082  23.753  1.00 19.15           O
HETATM 2416  O   HOH W  25      -2.293  55.387  20.951  1.00 19.34           O
HETATM 2417  O   HOH W  26      24.905  51.099  12.739  1.00 15.53           O
HETATM 2418  O   HOH W  27       5.194  61.579  14.666  1.00 19.85           O
HETATM 2419  O   HOH W  28      26.688  39.918  -9.461  1.00 18.05           O
HETATM 2420  O   HOH W  29      -4.828  59.634  25.600  1.00 17.12           O
HETATM 2421  O   HOH W  30       4.555  36.259  26.473  1.00 19.73           O
HETATM 2422  O   HOH W  31       2.529  32.398  17.591  1.00 17.16           O
HETATM 2423  O   HOH W  32      25.196  59.428  -8.087  1.00 17.22           O
HETATM 2424  O   HOH W  33      10.259  69.530 -15.733  1.00 18.49           O
HETATM 2425  O   HOH W  34      -5.495  49.278  22.481  1.00 18.77           O
HETATM 2426  O   HOH W  35      13.200  41.116  34.035  1.00 21.08           O
HETATM 2427  O   HOH W  36       7.124  69.221  21.128  1.00 19.75           O
HETATM 2428  O   HOH W  37      11.096  67.877  26.979  1.00 16.47           O
HETATM 2429  O   HOH W  38      20.313  54.738  33.912  1.00 17.96           O
HETATM 2430  O   HOH W  39       5.292  71.689  21.059  1.00 18.19           O
HETATM 2431  O   HOH W  40       5.131  56.479  14.657  1.00 17.35           O
HETATM 2432  O   HOH W  41       5.592  37.239  14.695  1.00 21.14           O
HETATM 2433  O   HOH W  42      -2.646  49.180  25.180  1.00 19.53           O
HETATM 2434  O   HOH W  43      18.978  37.507  -7.833  1.00 21.82           O
HETATM 2435  O   HOH W  44       6.177  62.808  34.479  1.00 19.85           O
HETATM 2436  O   HOH W  45      26.614  58.473   7.610  1.00 18.33           O
HETATM 2437  O   HOH W  46      13.874  61.347  36.062  1.00 23.02           O
HETATM 2438  O   HOH W  47       1.568  68.792   7.479  1.00 23.92           O
HETATM 2439  O   HOH W  48      25.877  45.862   6.070  1.00 20.75           O
HETATM 2440  O   HOH W  49      15.640  54.659   6.838  1.00 23.63           O
HETATM 2441  O   HOH W  50      20.971  56.183   8.467  1.00 18.33           O
HETATM 2442  O   HOH W  51      29.403  39.540  -9.354  1.00 20.57           O
HETATM 2443  O   HOH W  52       9.752  67.579   5.855  1.00 22.81           O
HETATM 2444  O   HOH W  53       5.675  43.021  28.715  1.00 19.15           O
HETATM 2445  O   HOH W  54      11.552  60.299  37.214  1.00 22.94           O
HETATM 2446  O   HOH W  55       8.846  64.765   6.410  1.00 23.10           O
HETATM 2447  O   HOH W  56      10.737  61.436 -10.110  1.00 20.69           O
HETATM 2448  O   HOH W  57      20.710  47.717  24.838  1.00 23.85           O
HETATM 2449  O   HOH W  58       6.577  57.159   1.317  1.00 22.88           O
HETATM 2450  O   HOH W  59       8.863  57.900  -0.207  1.00 22.83           O
HETATM 2451  O   HOH W  60      -7.001  51.952  24.530  1.00 26.02           O
HETATM 2452  O   HOH W  61      15.181  30.222  20.408  1.00 26.01           O
HETATM 2453  O   HOH W  62       9.734  67.562 -17.572  1.00 23.70           O
HETATM 2454  O   HOH W  63       7.452  72.773   9.664  1.00 25.11           O
HETATM 2455  O   HOH W  64      29.691  52.090  -2.811  1.00 29.20           O
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FIGURE 4OO

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HETATM 2456  O   HOH W  65      23.214  56.664   9.869  1.00 25.15           O
HETATM 2457  O   HOH W  66       9.978  41.338  34.428  1.00 23.35           O
HETATM 2458  O   HOH W  67      17.960  53.770   8.850  1.00 20.10           O
HETATM 2459  O   HOH W  68      27.843  54.821  18.015  1.00 25.79           O
HETATM 2460  O   HOH W  69       0.997  71.427   9.731  1.00 23.46           O
HETATM 2461  O   HOH W  70      25.317  37.682  -8.783  1.00 28.36           O
HETATM 2462  O   HOH W  71      13.075  58.354   2.682  1.00 20.02           O
HETATM 2463  O   HOH W  72      10.637  49.177  41.195  1.00 26.01           O
HETATM 2464  O   HOH W  73       6.040  54.611  40.359  1.00 25.36           O
HETATM 2465  O   HOH W  74      14.418  65.907  30.604  1.00 23.88           O
HETATM 2466  O   HOH W  75      -8.510  49.945  14.056  1.00 24.10           O
HETATM 2467  O   HOH W  76       8.863  56.217   8.553  1.00 27.89           O
HETATM 2468  O   HOH W  77      14.236  68.903   7.657  1.00 18.02           O
HETATM 2469  O   HOH W  78      13.673  73.981  19.313  1.00 23.06           O
HETATM 2470  O   HOH W  79       2.655  61.203  33.265  1.00 24.78           O
HETATM 2471  O   HOH W  80      16.081  49.559  38.301  1.00 22.19           O
HETATM 2472  O   HOH W  81      31.264  56.428  -3.845  1.00 28.22           O
HETATM 2473  O   HOH W  82      15.278  70.852  -9.834  1.00 23.37           O
HETATM 2474  O   HOH W  83      12.293  67.306  31.014  1.00 30.13           O
HETATM 2475  O   HOH W  84       1.153  67.896  23.680  1.00 26.47           O
HETATM 2476  O   HOH W  85       4.177  54.962  -5.513  1.00 26.51           O
HETATM 2477  O   HOH W  86       0.828  56.666  31.132  1.00 26.85           O
HETATM 2478  O   HOH W  87      28.043  58.100  16.860  1.00 25.80           O
HETATM 2479  O   HOH W  88       1.418  59.141  31.864  1.00 24.54           O
HETATM 2480  O   HOH W  89       5.171  72.267   6.832  1.00 24.31           O
HETATM 2481  O   HOH W  90      11.102  55.346   6.358  1.00 24.68           O
HETATM 2482  O   HOH W  91      24.301  57.703   7.432  1.00 30.45           O
HETATM 2483  O   HOH W  92      -9.909  65.963  19.571  1.00 23.47           O
HETATM 2484  O   HOH W  93       6.056  67.397   5.777  1.00 31.74           O
HETATM 2485  O   HOH W  94      -2.434  68.992  20.904  0.65 22.09           O
HETATM 2486  O   HOH W  95       8.275  64.974  36.309  1.00 27.28           O
HETATM 2487  O   HOH W  96       1.335  63.466  32.967  1.00 25.70           O
HETATM 2488  O   HOH W  97      -6.025  55.405  29.089  1.00 30.79           O
HETATM 2489  O   HOH W  98      10.185  36.392  30.992  1.00 31.63           O
HETATM 2490  O   HOH W  99      23.569  63.098  31.944  1.00 29.40           O
HETATM 2491  O   HOH W 100      -3.299  51.801  26.540  1.00 34.71           O
HETATM 2492  O   HOH W 101       6.351  62.723  -5.112  1.00 24.63           O
HETATM 2493  O   HOH W 102      14.594  69.684  20.375  1.00 24.27           O
HETATM 2494  O   HOH W 103      18.743  56.475   6.996  1.00 33.37           O
HETATM 2495  O   HOH W 104      12.569  39.880  15.153  1.00 30.55           O
HETATM 2496  O   HOH W 105      27.530  56.419   6.333  1.00 29.29           O
HETATM 2497  O   HOH W 106      26.134  39.160  -1.955  1.00 28.24           O
HETATM 2498  O   HOH W 107       2.711  60.861   7.995  1.00 27.06           O
HETATM 2499  O   HOH W 108       0.449  71.907  21.641  1.00 22.02           O
HETATM 2500  O   HOH W 109      24.328  60.651  -0.284  1.00 26.84           O
HETATM 2501  O   HOH W 110       0.105  36.807  21.145  1.00 35.25           O
HETATM 2502  O   HOH W 111       9.424  67.684   3.202  1.00 25.03           O
HETATM 2503  O   HOH W 112       9.870  65.101 -16.111  1.00 25.20           O
HETATM 2504  O   HOH W 113       0.331  62.672   7.998  1.00 25.35           O
HETATM 2505  O   HOH W 114      30.604  62.219  -3.326  1.00 31.23           O
HETATM 2506  O   HOH W 115      -8.461  62.947  13.452  1.00 31.44           O
HETATM 2507  O   HOH W 116       0.681  36.393  25.982  1.00 28.56           O
HETATM 2508  O   HOH W 117      15.503  50.561  40.707  1.00 28.73           O
HETATM 2509  O   HOH W 118      19.149  69.912  -4.488  1.00 26.57           O
HETATM 2510  O   HOH W 119      16.712  54.018   3.490  1.00 33.99           O
HETATM 2511  O   HOH W 120      14.544  43.323  35.404  1.00 30.45           O
HETATM 2512  O   HOH W 121       0.237  42.592  29.396  1.00 33.25           O
HETATM 2513  O   HOH W 122      22.577  64.264  25.463  1.00 25.91           O
HETATM 2514  O   HOH W 123      18.504  66.572  28.714  1.00 28.19           O
HETATM 2515  O   HOH W 124       6.514  43.992  34.159  1.00 32.12           O
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FIGURE 4PP

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HETATM 2516  O   HOH W 125      21.741  53.968  30.148  1.00 35.71           O
HETATM 2517  O   HOH W 126      20.388  60.636 -14.106  1.00 28.55           O
HETATM 2518  O   HOH W 127       3.717  52.185  -6.457  1.00 32.44           O
HETATM 2519  O   HOH W 128       4.097  75.012  20.095  1.00 26.13           O
HETATM 2520  O   HOH W 129      20.712  67.953   7.909  1.00 30.55           O
HETATM 2521  O   HOH W 130       2.616  71.475   7.389  1.00 32.66           O
HETATM 2522  O   HOH W 131      -3.968  46.144  35.287  1.00 27.82           O
HETATM 2523  O   HOH W 132      -6.231  58.370  29.959  1.00 34.83           O
HETATM 2524  O   HOH W 133      -9.573  70.666  20.525  1.00 35.61           O
HETATM 2525  O   HOH W 134      18.376  48.194 -10.777  1.00 31.13           O
HETATM 2526  O   HOH W 135       7.392  64.158 -14.488  1.00 28.92           O
HETATM 2527  O   HOH W 136      -9.806  64.044  22.839  1.00 30.94           O
HETATM 2528  O   HOH W 137      15.177  36.015  24.066  1.00 35.95           O
HETATM 2529  O   HOH W 138       0.207  36.075  18.248  1.00 30.22           O
HETATM 2530  O   HOH W 139      -5.121  66.714  13.239  1.00 30.64           O
HETATM 2531  O   HOH W 140      14.190  49.167  -9.420  1.00 34.64           O
HETATM 2532  O   HOH W 141       5.829  50.276   8.950  1.00 30.03           O
HETATM 2533  O   HOH W 142      -9.815  56.521   9.803  1.00 35.50           O
HETATM 2534  O   HOH W 143      21.370  40.122  30.064  1.00 39.91           O
HETATM 2535  O   HOH W 144       3.787  42.583  30.403  1.00 28.56           O
HETATM 2536  O   HOH W 145      10.595  57.142   1.988  1.00 27.77           O
HETATM 2537  O   HOH W 146       9.293  72.366  21.198  1.00 32.26           O
HETATM 2538  O   HOH W 147      18.066  45.436   6.890  1.00 38.15           O
HETATM 2539  O   HOH W 148      23.958  58.334  22.474  1.00 29.68           O
HETATM 2540  O   HOH W 149      16.270  43.356  10.738  1.00 33.04           O
HETATM 2541  O   HOH W 150      15.902  68.409   3.393  1.00 34.28           O
HETATM 2542  O   HOH W 151     -11.961  62.595  22.500  1.00 32.46           O
HETATM 2543  O   HOH W 152      -1.772  42.002  27.213  1.00 26.41           O
HETATM 2544  O   HOH W 153       8.485  49.605  -3.375  1.00 33.62           O
HETATM 2545  O   HOH W 154       6.448  64.907   5.091  1.00 35.35           O
HETATM 2546  O   HOH W 155      22.084  47.121  20.652  1.00 40.36           O
HETATM 2547  O   HOH W 156      31.367  37.760  -3.224  1.00 32.70           O
HETATM 2548  O   HOH W 157      23.401  64.152   1.455  1.00 32.23           O
HETATM 2549  O   HOH W 158      21.582  37.129  -8.471  1.00 29.98           O
HETATM 2550  O   HOH W 159      18.428  47.952   5.926  1.00 29.28           O
HETATM 2551  O   HOH W 160      17.740  53.594 -15.170  1.00 29.87           O
HETATM 2552  O   HOH W 161       3.010  72.509  22.439  1.00 32.98           O
HETATM 2553  O   HOH W 162      -2.553  63.775   6.938  1.00 38.56           O
HETATM 2554  O   HOH W 163      25.532  57.079 -11.112  1.00 35.81           O
HETATM 2555  O   HOH W 164      28.315  37.655  -1.292  1.00 32.11           O
HETATM 2556  O   HOH W 165      19.005  69.557   6.373  1.00 34.06           O
HETATM 2557  O   HOH W 166      26.973  52.660  11.997  1.00 40.44           O
HETATM 2558  O   HOH W 167      28.399  59.190   8.790  1.00 36.67           O
HETATM 2559  O   HOH W 168      12.457  68.215   0.508  1.00 32.73           O
HETATM 2560  O   HOH W 169      -6.664  47.822  33.009  1.00 30.45           O
HETATM 2561  O   HOH W 170     -10.120  66.890  17.047  1.00 37.90           O
HETATM 2562  O   HOH W 171      -6.174  74.062  17.486  1.00 37.11           O
HETATM 2563  O   HOH W 172      24.866  61.899  -9.630  1.00 33.35           O
HETATM 2564  O   HOH W 173      15.943  72.397   8.430  1.00 32.03           O
HETATM 2565  O   HOH W 174      13.398  49.109   8.104  1.00 35.44           O
HETATM 2566  O   HOH W 175      29.400  55.940   4.353  1.00 33.32           O
HETATM 2567  O   HOH W 176      30.471  49.195   8.045  1.00 37.82           O
HETATM 2568  O   HOH W 177      37.568  43.862  -4.195  1.00 41.27           O
HETATM 2569  O   HOH W 178       7.449  59.978  36.472  1.00 36.16           O
HETATM 2570  O   HOH W 179      -7.307  64.765  15.029  1.00 35.23           O
HETATM 2571  O   HOH W 180      12.538  46.698  39.295  1.00 36.56           O
HETATM 2572  O   HOH W 181      22.634  65.617  30.960  1.00 34.02           O
HETATM 2573  O   HOH W 182      -0.544  57.001  -5.760  1.00 34.80           O
HETATM 2574  O   HOH W 183      26.267  40.539   0.289  1.00 40.60           O
HETATM 2575  O   HOH W 184       3.841  35.275  15.463  1.00 36.73           O
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FIGURE 4QQ

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HETATM 2576  O   HOH W 185      25.012  64.020  18.977  1.00 34.92           O
HETATM 2577  O   HOH W 186      12.035  58.791 -17.936  1.00 45.62           O
HETATM 2578  O   HOH W 187      17.813  69.407  19.365  1.00 32.09           O
HETATM 2579  O   HOH W 188      21.592  69.401 -10.464  1.00 35.28           O
HETATM 2580  O   HOH W 189       3.273  73.522  24.886  1.00 38.36           O
HETATM 2581  O   HOH W 190       6.976  76.851  10.508  1.00 38.77           O
HETATM 2582  O   HOH W 191       8.681  74.921  10.334  1.00 38.77           O
HETATM 2583  O   HOH W 192      27.748  49.411   9.534  1.00 40.05           O
HETATM 2584  O   HOH W 193      25.094  45.375  11.303  1.00 38.80           O
HETATM 2585  O   HOH W 194      14.543  69.038  24.470  1.00 32.84           O
HETATM 2586  O   HOH W 195      32.510  54.900  -9.840  1.00 45.77           O
HETATM 2587  O   HOH W 196       8.698  67.456  -5.183  1.00 35.92           O
HETATM 2588  O   HOH W 197      16.502  69.545   5.737  1.00 38.64           O
HETATM 2589  O   HOH W 198      -7.354  63.246  11.247  1.00 39.32           O
HETATM 2590  O   HOH W 199     -12.028  68.718  21.648  1.00 33.50           O
HETATM 2591  O   HOH W 200      -6.896  67.904  14.804  1.00 39.42           O
HETATM 2592  O   HOH W 201      24.429  58.682  28.796  1.00 32.80           O
HETATM 2593  O   HOH W 202      20.994  45.374  22.270  1.00 43.18           O
HETATM 2594  O   HOH W 203      27.768  36.163   0.789  1.00 37.93           O
HETATM 2595  O   HOH W 204      12.107  70.493   5.353  1.00 31.16           O
HETATM 2596  O   HOH W 205       8.004  80.542  17.728  1.00 38.22           O
HETATM 2597  O   HOH W 206       7.479  80.021  13.490  1.00 34.21           O
HETATM 2598  O   HOH W 207      11.897  75.857  22.951  1.00 41.33           O
HETATM 2599  O   HOH W 208      19.816  71.916  17.196  1.00 44.96           O
HETATM 2600  O   HOH W 209      25.642  64.112  -8.802  1.00 44.32           O
HETATM 2601  O   HOH W 210      18.952  66.778  25.999  1.00 37.54           O
HETATM 2602  O   HOH W 211      -0.655  38.452  17.557  1.00 38.45           O
HETATM 2603  O   HOH W 212     -12.764  62.388   9.560  1.00 36.35           O
HETATM 2604  O   HOH W 213      21.845  74.994  14.861  1.00 41.32           O
HETATM 2605  O   HOH W 214      30.786  53.281   7.250  1.00 44.09           O
HETATM 2606  O   HOH W 215       7.793  52.413   8.548  1.00 41.95           O
HETATM 2607  O   HOH W 216      30.863  53.890   4.624  1.00 38.22           O
HETATM 2608  O   HOH W 217      -4.781  72.462  14.360  1.00 41.00           O
HETATM 2609  O   HOH W 218      -0.870  68.104   6.236  1.00 39.73           O
HETATM 2610  O   HOH W 219      13.650  58.218  39.241  1.00 40.58           O
HETATM 2611  O   HOH W 220       1.493  66.322   6.500  1.00 45.88           O
HETATM 2612  O   HOH W 221      23.567  56.278 -16.417  1.00 34.33           O
HETATM 2613  O   HOH W 222      23.046  34.837  17.272  1.00 39.62           O
HETATM 2614  O   HOH W 223      -8.109  59.892  28.916  1.00 37.82           O
HETATM 2615  O   HOH W 224      10.352  42.254   9.975  1.00 39.29           O
HETATM 2616  O   HOH W 225      18.885  35.203  16.703  1.00 44.51           O
HETATM 2617  O   HOH W 226      12.946  69.611  26.650  1.00 34.69           O
HETATM 2618  O   HOH W 227       7.058  35.692  13.366  1.00 37.88           O
HETATM 2619  O   HOH W 228     -13.267  54.430  15.645  1.00 23.80           O
HETATM 2620  O   HOH W 229      12.963  69.458  -3.453  1.00 35.08           O
HETATM 2621  O   HOH W 230      33.510  49.606  -4.025  1.00 30.23           O
HETATM 2622  O   HOH W 231      16.160  59.023  39.473  1.00 35.64           O
HETATM 2623  O   HOH W 232      12.557  56.102  40.090  1.00 43.14           O
HETATM 2624  O   HOH W 233      13.800  72.882  10.589  1.00 34.37           O
HETATM 2625  O   HOH W 234      20.533  67.069  23.261  1.00 37.64           O
HETATM 2626  O   HOH W 235      17.817  67.874  23.169  1.00 43.45           O
HETATM 2627  O   HOH W 236      10.472  63.084 -17.699  1.00 44.86           O
HETATM 2628  O   HOH W 237      24.573  38.270  21.430  1.00 35.75           O
HETATM 2629  O   HOH W 238      12.284  67.555  -2.962  1.00 38.23           O
HETATM 2630  O   HOH W 239      14.642  70.486  -3.593  1.00 41.27           O
HETATM 2631  O   HOH W 240      12.690  72.444  -4.729  1.00 38.59           O
HETATM 2632  O   HOH W 241      10.269  78.965  17.530  1.00 34.88           O
END
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FIGURE 4RR

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